Λ66

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 October 2000 (05.10.2000)

PCT

(10) International Publication Number
WO 00/57877 A1

(51) International Patent Classification[7]: A61K 31/40, 31/415, 31/421, 31/426, 31/496, 31/506, 31/4164, 31/5377, C07D 207/30, 231/10, 233/54, 403/00, 413/00

(21) International Application Number: PCT/US00/07944

(22) International Filing Date: 24 March 2000 (24.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/126,553 26 March 1999 (26.03.1999) US

(71) Applicant *(for all designated States except US)*: COCENSYS, INC. [US/US]; 213 Technology Drive, Irvine, CA 92618 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HOGENKAMP, Derk, J. [US/US]; 4510 Park Drive, Carlsbad, CA 92008 (US). UPASANI, Ravindra [IN/US]; 63 Montecilo, Foothill Ranch, CA 92610 (US). NGUYEN, Phong [US/US]; 1048 Wingfoot Street, Placentia, CA 92870 (US).

(74) Agents: COVERT, John, M.; Sterne, Kessler, Goldstein & Fox P.L.L.C., Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE (utility model), DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

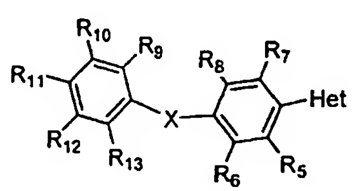
Published:
— *With international search report.*

(48) Date of publication of this corrected version:
5 April 2001

(15) Information about Correction:
see PCT Gazette No. 14/2001 of 5 April 2001, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ARYL SUBSTITUTED PYRAZOLES, IMIDAZOLES, OXAZOLES, THIAZOLES AND PYRROLES, AND THE USE THEREOF



(I)

(57) Abstract: This invention relates to compounds having Formula (I) or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein Het and R_5-R_{13} are set in the specification. The invention also is directed to the use of compounds of Formula (I) for the treatment of neuronal damage following global and focal ischemia, for the treatment or prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), and for the treatment, prevention or amelioration of both acute or chronic pain, as antitinnitus agents, as anticonvulsants, and as antimanic depressants, as local anesthetics, as antiarrhythmics and for the treatment or prevention of diabetic neuropathy.

WO 00/57877 A1

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Aryl Substituted Pyrazoles, Imidazoles, Oxazoles, Thiazoles and Pyrroles, and the Use Thereof

Background of the Invention

Field of the Invention

This invention is in the field of medicinal chemistry. In particular, the invention relates to aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles, and the discovery that these compounds are anticonvulsants and act as blockers of sodium (Na^+) channels.

Related Background Art

Several classes of therapeutically useful drugs, including local anesthetics such as lidocaine and bupivacaine, antiarrhythmics such as propafenone and amioclarone, and anticonvulsants such as lamotrigine, phenytoin and carbamazepine, have been shown to share a common mechanism of action by blocking or modulating Na^+ channel activity (Catterall, W.A., *Trends Pharmacol. Sci. 8*:57-65 (1987)). Each of these agents is believed to act by interfering with the rapid influx of Na^+ ions.

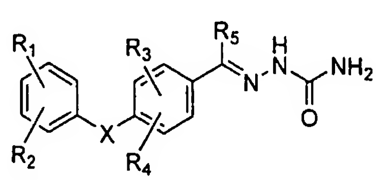
Recently, other Na^+ channel blockers such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia and are presently in clinical trials (Graham *et al., J. Pharmacol. Exp. Ther.* 269:854-859 (1994); Brown *et al., British J. Pharmacol. 115*:1425-1432 (1995)).

The neuroprotective activity of Na^+ channel blockers is due to their effectiveness in decreasing extracellular glutamate concentration during ischemia by inhibiting the release of this excitotoxic amino acid neurotransmitter. Studies have

shown that unlike glutamate receptor antagonists, Na^+ channel blockers prevent hypoxic damage to mammalian white matter (Stys *et al., J. Neurosci. 12*:430-439 (1992)). Thus, they may offer advantages for treating certain types of strokes or neuronal trauma where damage to white matter tracts is prominent.

Another example of clinical use of a Na^+ channel blocker is riluzole. This drug has been shown to prolong survival in a subset of patients with ALS (Bensim *et al., New Engl. J. Med. 330*:585-591 (1994)) and has subsequently been approved by the FDA for the treatment of ALS. In addition to the above-mentioned clinical uses, carbamazepine, lidocaine and phenytoin are occasionally used to treat neuropathic pain, such as from trigeminal neurologia, diabetic neuropathy and other forms of nerve damage (Taylor and Meldrum, *Trends Pharmacol. Sci. 16*:309-316 (1995)), and carbamazepine and lamotrigine have been used for the treatment of manic depression (Denicott *et al., J. Clin. Psychiatry 55*: 70-76 (1994)). Furthermore, based on a number of similiarities between chronic pain and tinnitus (Moller, A. R. *Am. J. Otol. 18:* 577-585 (1997); Tonndorf, *J. Hear. Res. 28:* 271-275 (1987)) it has been proposed that tinnitus should be viewed as a form of chronic pain sensation (Simpson, J. J. and Davies, E. W. *Tip. 20:* 12-18 (1999)). Indeed, lignocaine and carbamazepine have been shown to be efficacious in treating tinnitus (Majumdar, B. *et al. Clin. Otolaryngol. 8:* 175-180 (1983); Donaldson, I. *Laryngol. Otol. 95:* 947-951 (1981)).

It has been established that there are at least five to six sites on the voltage-sensitive Na^+ channels which bind neurotoxins specifically (Catterall, W.A., *Science 242*:50-61 (1988)). Studies have further revealed that therapeutic antiarrhythmics, anticonvulsants and local anesthetics whose actions are mediated by Na^+ channels, exert their action by interacting with the intracellular side of the Na^+ channel and allosterically inhibiting interaction with neurotoxin receptor site 2 (Catterall, W.A., *Ann. Rev. Pharmacol. Toxicol. 10*:15-43 (1980)).

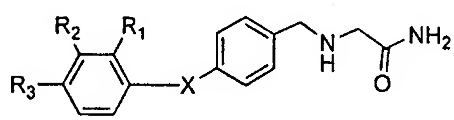


PCT International Published Application WO96/40628 discloses semicarbazones represented by the following Formula:

where R_1-R_4 are independently hydrogen, halogen, C_{1-9} alkyl, C_{3-9} cycloalkyl, cyano, C_{1-9} alkoxy, or C_{6-10} aryloxy; R_5 is hydrogen, C_{1-9} alkyl, C_{3-9} cycloalkyl, or C_{6-10} aryl; and X is oxygen or sulfur. The compounds are disclosed to be useful as anticonvulsants.

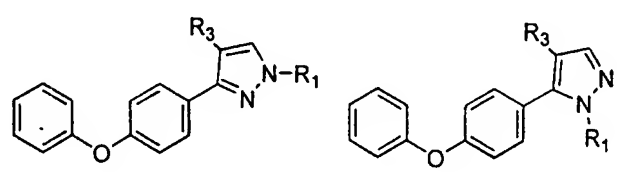
Dimmock *et al.*, (*J. Med. Chem.* *39*:3984-3997 (1996)) discloses (aryloxy)aryl semicarbazones that displayed anticonvulsant activities when administered intraperitoneally to mice or orally to rats.

Pevarello *et al.*, (*J. Med. Chem.* *41*:579-590 (1998)) discloses 2-[(arylalkyl)amino]alkanamide derivatives represented by the following Formula:



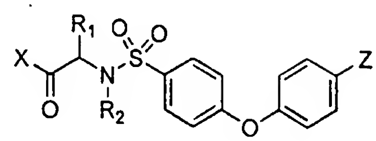
where R_1 is chloro, fluoro, trifluoromethyl, R_2 is chloro, cyano, fluoro, methyl, nitro, methoxy and trifluoromethyl, R_3 is chloro and fluoro and X is CH_2O, a bond, CH_2, CH_2CH_2, CH_2S, CH_2NH, OCH_2, CH_2CH_2O, $CH_2CH_2CH_2O$, $CH_2N(Me)$, $NHCH_2$, CONH and CH=CH. The compounds are disclosed to be useful as anticonvulsants due to activity as sodium channel blockers.

PCT International Published Application WO 98/52940 discloses substituted pyrazoles of the following Formulae:



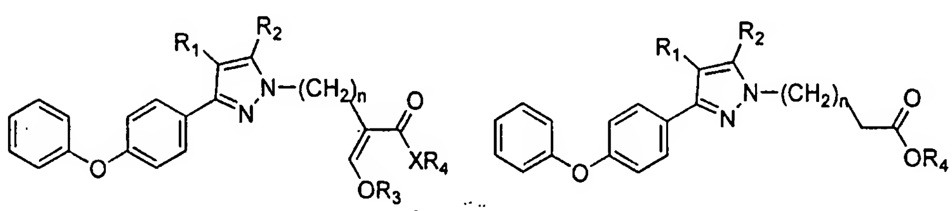
where R_1 is alkylsulfinyl, arylsulfinyl, alkylsulfonyl and acyl and R_3 is limited to pyridinyl, pyrimidinyl, quinolinyl, purinyl, C-attached malemides and pyridiones. The compounds are disclosed to be useful as p38 kinase inhibitors.

PCT International Published Application WO 98/50348 discloses substituted sulfonamides of the following Formula:



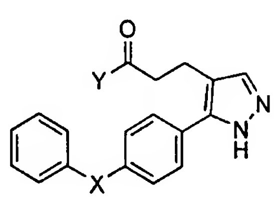
where Z is a heteroaryl group. The compounds are disclosed to be metalloproteinase inhibitors.

Japanese Patent Application JP 10168063 (CA 129:91737) discloses compounds of the following Formulae:



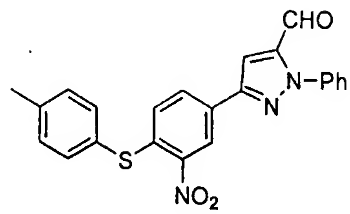
The compounds are described as microbiocides.

European Patent Application EP 446180 discloses substituted pyrazoles of the following Formula:

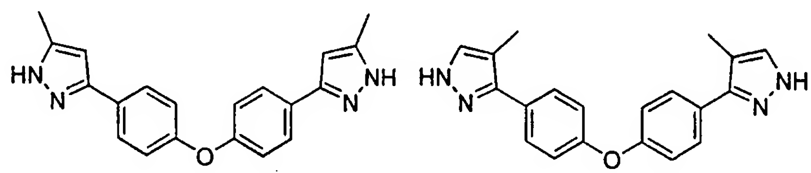


wherein X is oxygen and Y is OC_2H_5 or OH. The compounds are disclosed as starting materials.

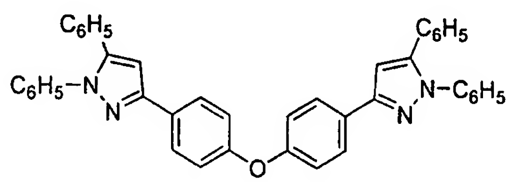
Radwan, S. M. (*Collect. Czech. Chem. Commun. 57(7):* 1553-1558 (1992)) describes the synthesis of the compound of the following Formula:



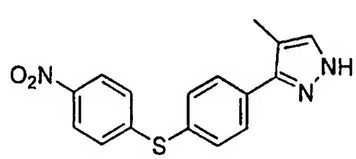
Korshak, K. K., *et al., (Polym. Sci. USSR (Engl. Transl.) 6:* 1087, 1196-1198 (1964) and *J. Polym. Sci. Part A 3*: 2425-2439 (1965)) describe the synthesis of the following compounds:



Stille *et al.,* (*J. Polym. Sci. Part A-1* 6: 2317-2330 (1968)) describe the synthesis of the following compound:

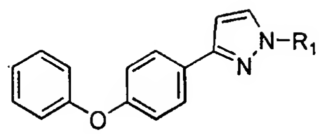


Szmant *et al.*, (*J. Am. Chem. Soc. 78*: 4386-4389 (1956)) describes the following compound:



Grandberg *et al.* (*J. Gen. Chem. USSR (Engl. Transl) 30*: 1404-1408 (1960)) describe the synthesis of 3-(4-phenoxyphenyl)pyrazoles of the following

Formula:

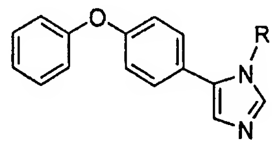


where R_1 is hydrogen or $C(O)NH_2$. With R_1 hydrogen, the picrate salt was also prepared.

The following pyrazoles are part of the available chemical directory (ACD):

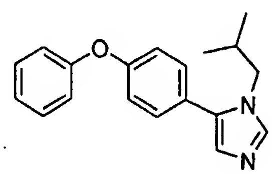
2-chloro-6-[4-(1H-pyrazol-5-yl)phenoxy]benzonitrile; 2-chloro-6-[4-(1-methyl-1H-pyrazol-5-yl)phenoxy]benzonitrile; 2-chloro-6-[4-[1-(4-chlorobenzoyl)-1H-pyrazol-5-yl]phenoxy]benzonitrile; 2-[4-(1-acetyl-1H-pyrazol-5-yl)phenoxy]-6-chlorobenzonitrile; 2-chloro-6-(4-[1-[(4-chlorophenyl)sulfonyl]-1H-pyrazol-5-yl]phenoxy)benzonitrile; 2-chloro-6-[4-[1-(methylsulfonyl)-1H-pyrazol-5-yl]phenoxy]benzonitrile; 2-chloro-6-[4-[1-(4-chlorophenyl)-1H-pyrazol-3-yl]phenoxy]benzonitrile; 3-(4-phenoxyphenyl)-1H-pyrazole; 3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole; 3-[4-(4-methoxyphenoxy)phenyl]-1H-pyrazole; 3-[4-(phenylthio)phenyl]-1H-pyrazole; 3-[4-(phenylsulfonyl)phenyl]-1H-pyrazole; 5-(methylthio)-3-(4-phenoxyphenyl)-1H-pyrazole; N1-phenyl-5-(methylthio)-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide; (4-chlorophenyl)[5-(methylthio)-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl]methanone; N1-(4-chlorophenyl)-5-(methylthio)-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide; [5-(methylthio)-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl](phenyl)methanone; 3-(2-chloro-4[4-chlorophenoxy])phenyl pyrazole; 1-phenylcarbamoyl-3-(2-chloro-4-[4-chlorophenoxy]phenyl pyrazole; 3-(2-chloro-4[4-chlorophenoxy])phenyl-1-(4-chlorophenylcarbamoyl)pyrazole; 3-(2-chloro-4[4-chlorophenoxyl]phenyl-1-(4-chlorobenzoyl)pyrazole;1-(4-chlorobenzenesulfonyl-3-(2-chloro-4-[4-chlorophenoxy]phenylpyrazole; 1-(2,4-dichlorophenylsulfonyl)-3-dimethylamino-4-(4-phenoxyphenyl)-pyrazole; N1-phenyl-5-morpholino-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide; 3-chloro-2-[5-[4-(phenylthio)phenyl]-1H-pyrazol-1-yl]-5-(trifluoromethyl)-pyridine and 2-chloro-6-[4-(1-methyl-1H-pyrazol-3-yl)phenoxy]-benzonitrile.

Yamada *et al.* describe in *Biosci. Biotechnol. Biochem.* 56:1943-1948 (1992) the synthesis of the compounds of the following formula:



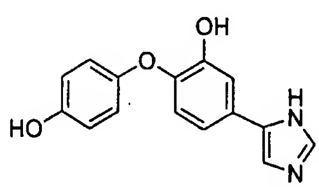
wherein R is H or Et. The compounds were inactive as bleaching agents in lettuce seedlings.

Kuwano *et al.* (*Agric. Biol. Chem.* 55:2999-3004 (1991)) describe the synthesis of the compound of the formula:

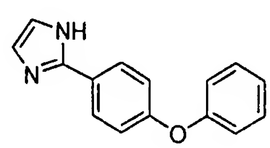


The compound is described as an insecticide.

Walker *et al.* (*J. Chem. Soc.* 347-350 (1942) describe the following compound as its picrate salt:



Schubert *et al.* (*J. Prakt. Chem.* 18 (No. 3-4): 192-202 (1962)) describes a compound of formula:



European Patent Application No. 269238 describes 2-(4-phenoxyphenyl)-1H-imidazole-4,5-dicarbonitrile and 5-cyano-2-(4-phenoxyphenyl)-1H-imidazole-4-carboxamide as plant growth regulators.

WO 99/11627, JP 05287563, JP 59075257, Todorova *et al.* (*Tr. Nauchnoizsled. Khim.-Farm. Inst.* 10: 85-94 (1978)), and Vodenicharov *et al.* (*Dokl. Bolg. Akad. Nauk.* 31(4): 441-444 (1978)) describe substituted benzimidazole derivatives.

Golanova *et al.* (*Zh. Org. Khim.* 29:1319-1324 (1993)), Ermikow *et al.* (*Z. Obshch. Khim.* 58: 450-457 (1988)), and Trofimov *et al.* (*Khim. Geterotsikl. Soedin.* 4: 489-491 (1978)) disclose 2-(4-phenoxyphenyl)-1H-pyrrole. No pharmaceutical use is described or suggested.

JP 07025849 describes a method for preparing 5-(4-phenoxyphenyl)-2-(trifluoromethyl)-1H-pyrrole-3-carbonitrile which is stated to be useful as intermediate for agrochemicals and pharmaceuticals.

Korostova *et al.* (*Khim. Geterotsikl. Soedin.* 5: 609-613 (1992)) disclose the synthesis of 2-[4-(phenylthio)phenyl]-1H-pyrrole.

Anderson *et al.* (*J. Med. Chem.* 22: 977-980 (1979)) disclose substituted 1,2-dimethyl-5-[4-(phenylthio)]-1H-pyrroles and 1,2-dimethyl-5-[4-(phenylsulfonyl)]-1H-pyrroles that have antileukemic activity.

WO 93/23374 describes the preparation of several indole derivatives that are stated to have antiestrogenic properties.

Dann *et al.* (*Liebigs Ann. Chem.* 3: 409-425 (1984)) discloses several indole derivatives having antimicrobial activity.

2-[4-[3-(Aminoiminomethyl)phenoxy]phenyl]-1H-indole-6-carboximidamide has been reported to have antihyperpensive, antitumor, antifertility, antifungal and antibacterial properties.

Compounds of Formula ***I*** have not been used heretofor for treating a disorder responsive to the blockade of sodium channels in a mammal.

Summary of the Invention

The present invention is related to the discovery that aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles represented by Formula ***I*** are anticonvulsants and act as blockers of sodium (Na^+) channels.

The invention is also related with treating a disorder responsive to the blockade of sodium channels in a mammal suffering from excess activity of said channels by administering an effective amount of a compound of Formula ***I*** as described herein.

The present invention is also directed to the use of a compound of Formula ***I*** for the treatment of neuronal damage following global and focal ischemia, and for the treatment or prevention of neurodegenerative conditions, such as amyotrophic lateral sclerosis (ALS), for the treatment of tinnitus, as antimanic depressants, as local anesthetics, as antiarrhythmics, as anticonvulsants and for the treatment or prevention of diabetic neuropathy and for the treatment of pain including both acute and chronic pain and migraine headache.

Another aspect of the present invention is directed to the use of the compounds of Formula ***I*** as blockers of sodium channels.

A third aspect of the present invention is to provide a method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating pain including acute and chronic pain, and neuropathic pain; treating, preventing or ameliorating convulsion and neurodegenerative conditions; treating, preventing or ameliorating manic depression; using as local anesthesics, antiarrhythmics, and treating tinnitus by administering a compound of Formula ***I*** to a mammal in need of such treatment.

A further aspect of the present invention is to provide a pharmaceutical composition useful for treating disorders responsive to the blockade of sodium ion channels, containing an effective amount of a compound of Formula ***I*** in a mixture with one or more pharmaceutically acceptable carriers or diluents.

A number of compounds useful in the present invention have not been heretofor reported. Thus, the present invention is also directed to novel aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles of Formula ***I***.

Further, the present invention is directed to ^{3}H and ^{14}C radiolabeled compounds of Formula ***I*** and their use as radioligands for their binding site on the sodium channel.

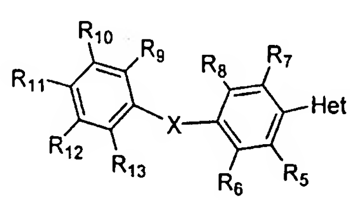
Additional embodiments and advantages of the invention will be set forth in part of the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

Detailed Description of the Invention

The present invention arises out of the discovery that the aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles of Formula ***I*** are anticonvulsants and act as blockers of Na^{+} channels. In view of this discovery, compounds of Formula ***I*** are useful for treating disorders responsive to the blockade of sodium ion channels.

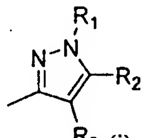
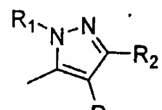
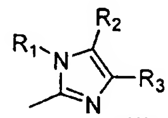
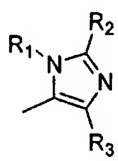
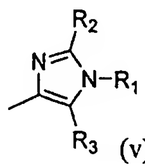
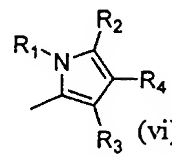
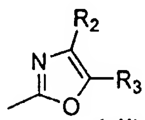
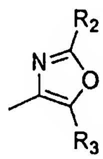
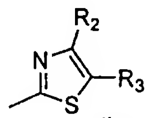
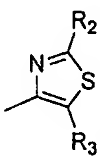
The compounds useful in this aspect of the present invention are the aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles represented by Formula ***I***:



I

a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Het is a heteroaryl selected from the group consisting of


(i) ;

(ii) ;

(iii) ;

(iv) ;

(v) ;

(vi) ;

(vii) ;

(viii) ;

(ix) and

(x) ;

R_1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14} all of which may be optionally substituted;

R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, cyano, amino, alkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, or the R groups in adjacent carbon atoms can be taken together with the carbon atoms to which they are

attached to form a carbocycle or a heterocycle. Examples of bridges formed by R groups taken together are

—OCH_2O—, —OCF_2O—, —$(CH_2)_3$—, —$(CH_2)_4$—, —OCH_2CH_2O—, —$CH_2N(R_{15})CH_2$—, —$CH_2CH_2N(R_{15})CH_2$—, —$CH_2N(R_{15})CH_2CH_2$— and —CH=CH—CH=CH—; where R_{15} is hydrogen, alkyl, or cycloalkyl;

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; or R_9 and R_{10} or R_{10} and R_{11} are taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle. Examples of bridges formed by R_9 and R_{10} or R_{10} and R_{11} taken together are

—OCH_2O—, —OCF_2O—, —$(CH_2)_3$—, —$(CH_2)_4$—, —OCH_2CH_2O—, —$CH_2N(R_{15})CH_2$—, —$CH_2CH_2N(R_{15})CH_2$—, —$CH_2N(R_{15})CH_2CH_2$— and —CH=CH—CH=CH—; where R_{15} is defined as above;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkynyl, arylalkylamino, dialkylaminoalkenyl, heterocycle, heterocycloalkylamino, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$, where R_{15} is defined as above.

One group of useful compounds of the invention are compounds of the general Formula *I*, wherein Het is (i)-(vi), R_1-R_{16} and X are as defined above with the following provisos that:

1) when Het is (i) or (ii),

a) R_1 is H and X is O or S, at least one of R_2, R_3 and R_5-R_{13} is other than H, except that R_{11} is not NO_2 when R_3 is CH_3, and R_3 is not $-CH_2CH_2COOH$ when the other substituents are each H;

b) R_1 is H, X is O and one of R_9-R_{13} is NO_2 or OCH_3, at least one the other substituents is other than H;

c) X is O, R_9 or R_{13} is CN and a Cl group is *ortho* to CN, at least one of R_2, R_3 and R_5-R_8 is other than H;

d) X is O, R_5 and R_{11} are Cl, at least one of R_6, R_7, R_8, R_9, R_{10}, R_{12} and R_{13} is other than H;

e) X is O, R_2 is methylthio, R_1 is H or $C(O)R_{14}$ wherein R_{14} is optionally substituted phenyl, at least one of R_5-R_{13} is other than H; or

f) R_1 is $C(O)NH_2$ and X is O, at least one of R_2, R_3 and R_5-R_{13} is other than H;

2) when Het is (iii),

a) R_1 is H, X is O or CH_2 and R_2 and R_3 together form $-CH=CH-CH=CH-$, R_5-R_{13} are not all H;

b) R_1 is Et and R_2 and R_3 together form $-CH=CH-CH=CH-$, X is not -NEt; or

c) R_1 is H and X is O, R_2-R_{13} are not all H;

3) when Het is (iv) and R_1 is H or alkyl, R_2-R_{13} are not all H; or

4) when Het is (vi),

a) X is O, S, or CH_2, R_2 and R_4 do not together form $-CH=CH-CH=CH-$;

b) R_1 is H and X is O or S, R_2-R_{13} are not all H; or

c) X is S and R_1 and R_2 both are Me, at least one of R_3 and R_4 is other than $-CH_2OH$.

One group of preferred compounds falling within the scope of Formula ***I*** include compounds wherein R_1 is $C(O)R_{14}$ or SO_2R_{14}, where R_{14} is amino or C_{1-6} alkyl and X is O or S.

One group of preferred compounds falling within the scope of Formula *I* include compounds wherein R_1 is optionally substituted heteroaryl, optionally substituted C_{1-6} alkyl, or $CH_2C(O)R_{14}$, wherein R_{14} is an optionally substituted heterocycle, such as N-morpholinyl, N-pyrrolidinyl or N-piperazinyl, optionally substituted C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, or OR_{16}, wherein R_{16} is C_{1-6} alkyl.

One group of preferred compounds falling within the scope of Formula *I* include compounds wherein Het is selected from the group consisting of (i), (ii), (iv) and (v).

When Het is (iii), (iv) or (v), R_1 is preferably H or alkyl and R_2 and R_3 are both hydrogen.

Preferably, when Het is (vi), R_1 is hydrogen, R_2 is selected from the group consisting of aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, preferably aminocarbonyl, and R_3 and R_4 are both hydrogen.

One group of preferred compounds falling within the scope of Formula *I* include compounds wherein Het is selected from the group consisting of (vii), (viii), (ix) and (x).

Preferably, R_1 is selected from the group consisting of an alkyl optionally substituted by halogen, hydroxy, carbamoyloxy, C_{1-6} acyl, C_{1-6} alkylsulfonylamino, aryl, preferably phenyl, or aminocarbonyl, heteroaryl, preferably pyrimidine, $C(O)R_{14}$, $CH_2C(O)R_{14}$, or SO_2R_{14}, wherein R_{14} is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, OR_{16}, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkenylamino, di(C_{1-6})alkylaminoalkenyl, heterocycle, and heterocyclo(C_{1-6})alkylamino, all of which can be optionally substituted, and wherein R_{16} is as defined above.

Preferably, R_{14} is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, OR_{16}, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkenylamino, di(C_{1-6})alkylamino(C_{2-6})alkenyl, heterocycle, and heterocyclo(C_{1-6})alkylamino, all of which can be optionally substituted, wherein R_{16} is as defined above.

Preferably, R_2-R_4 are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, amino(C_1-C_6)alkyl, amino, C_1-C_6 alkylthio, cyano, C_1-C_6 alkylsulfinyl, hydroxy(C_1-C_6)alkyl, C_1-C_6 alkoxy, aminocarbonyl, C_1-C_6 alkylaminocarbonyl, C_6-C_{10} arylaminocarbonyl, C_6-C_{10} aryl(C_1-C_6)alkylamino-carbonyl, C_1-C_6 alkylcarbonylamino, C_6-C_{10} arylcarbonylamino, C_6-C_{10} aryl(C_1-C_6)alkylcarbonylamino, C_1-C_6 alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, C_1-C_6 alkylaminosulfonyl, C_1-C_6 alkylsulfonyl, and heterocyclosulfonyl, more preferably hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino (C_1-C_6)alkyl, C_1-C_6 alkylthio and aminocarbonyl.

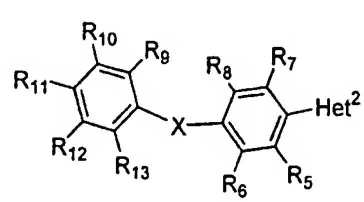
Preferred values of R_5-R_{13} include hydrogen, halo, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_4-C_7 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl(C_1-C_6)alkyl, C_6-C_{10} aryl(C_2-C_6)alkenyl, C_6-C_{10} aryl(C_2-C_6)alkynyl, C_1-C_6 hydroxyalkyl, nitro, amino, ureido, cyano, C_1-C_6 acylamido, hydroxy, thiol, C_1-C_6 acyloxy, azido, C_1-C_6 alkoxy, or carboxy. The groups R_5-R_{13} each take place of a hydrogen atom that would otherwise be present in any position on the aryl ring to which the R group is attached.

Especially preferred are compounds where R_5-R_8 are all hydrogen.

Preferably X is O or S, more preferably X is O.

Preferably, R_3 and R_4 are both H.

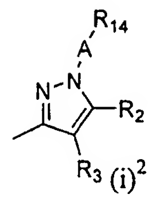
Another group of useful compounds of this invention are those having the Formula ***II***:

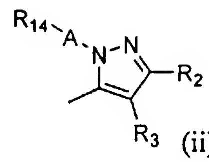


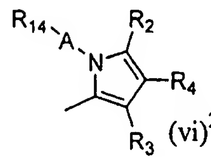
II

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

Het[2] is selected from the group consisting of


(i)^2 ;


(ii)^2 and


(vi)^2 ;

A is selected from the group consisting of C(O), $CH_2C(O)$, S(O) and SO_2;

R_{2-15} are as defined previously with respect to Formula *I*; and

X is O or S,

with the proviso that when Het^2 is (i)^2 or (ii)^2

a) X is O, R_2 is methylthio, R_1 is H or $C(O)R_{14}$ wherein R_{14} is optionally substituted phenyl, at least one of R_5-R_{13} is other than H; or

b) R_1 is $C(O)NH_2$ and X is O, at least one of R_2, R_3 and R_5-R_{13} is other than H.

Especially preferred compounds with respect to Formula *II* include those wherein:

R_{14} is amino, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylamino or optionally substituted heterocycle, such as N-morpholinyl, N-pyrrolidinyl and N-piperazinyl;

R_2, R_3, and R_4 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylthio or C_1-C_6 alkylsulfinyl; and

X is O;

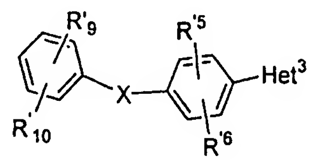
with the proviso that the compound is not 3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide.

Also, preferred compounds of Formula *II* include those where A is C(O) or $CH_2C(O)$, X is O and R_{14}, R_2, R_3, and R_4 are as defined above.

Further, preferred compounds of Formula *II* include those where A is S(O) or SO_2, preferably SO_2, R_2-R_4 are independently H or C_{1-6} alkyl and X is O. Also,

preferred compounds of Formula *II* include those where A is S(O) or SO_2, preferably SO_2, R_2-R_4 are H, R_{14} is methyl and X is O.

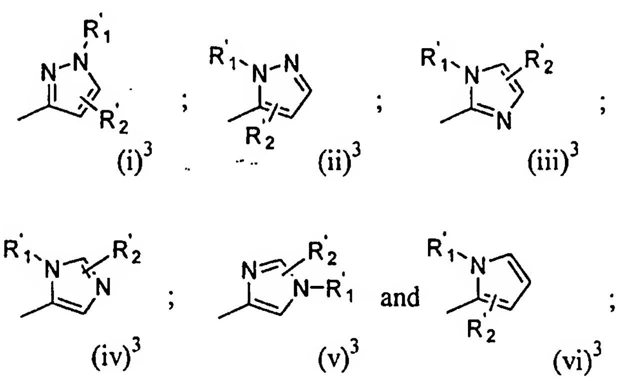
Further another group of useful compounds of the invention are those having the Formula *III*:



III

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

Het^3 is selected from the group consisting of



R'_1 is selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14};

R'_2 is attached to a carbon atom that is not the linking atom attached to the aryl group and is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cyano, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl;

R'_5, R'_6, R'_9, and R'_{10} are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkenyl, heterocycle, heterocycloalkyl, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$ where R_{15} is defined as above, with the following provisos that:

1) when Het is $(i)^3$ or $(ii)^3$,

a) R'_1 is H and X is O or S, at least one of R'_2, R'_5, R'_6, R'_9 and R'_{10} is other than H, except that R'_9 or R'_{10} is not NO_2 when R'_2 is CH_3, and R'_2 is not $-CH_2CH_2COOH$ when the other substituents are each H;

b) R'_1 is H, X is O and R'_9 or R'_{10} is NO_2 or OCH_3, at least one of the other substituents is other than H;

c) X is O, R'_9 and R'_{10} are CN and a Cl group *ortho* to CN, at least one of R'_2, R'_5 or R'_6 is other than H;

d) X is O, R'_5 and R'_9 are Cl, at least one of R'_6 or R'_{10} is other than H;

e) X is O, R'_2 is methylthio, R'_1 is H or $C(O)R_{14}$ wherein R_{14} is optionally substituted phenyl, at least one of R'_5, R'_6, R'_9 or R'_{10} is other than H; or

f) R'_1 is $C(O)NH_2$ and X is O, at least one of R'_2, R'_5, R'_6, R'_9 or R'_{10} is other than H;

2) when Het is $(iii)^3$, R'_1 is H and X is O, R'_5, R'_6, R'_9 or R'_{10} are not all H;

3) when Het is $(iv)^3$ and R'_1 is H or alkyl, R'_5, R'_6, R'_9 or R'_{10} are not all H; or

4) when Het is $(vi)^3$, R'_1 is H and X is O or S, R'_5, R'_6, R'_9 or R'_{10} are not all H.

Preferably X is O or S in compounds of Formula *III*.

Preferably, when Het^3 is $(i)^3$ or $(ii)^3$, R'_1 is heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, or SO_2R_{14} wherein R_{14} is amino, alkyl, alkylamino or heterocycle, more preferably amino, all of which can be optionally substituted. When R'_2 is aminocarbonyl, R'_1 is preferably hydrogen.

Preferably, when Het^3 is $(vi)^3$, R'_1 is hydrogen and R'_2 is selected from the group consisting of aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, preferably aminocarbonyl.

Preferably, when Het^3 is $(iii)^3$, $(iv)^3$ or $(v)^3$, R'_1 is hydrogen or alkyl, and R'_2 is hydrogen.

Preferably, R'_2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, carboxy(C_1-C_6)alkyl, C_1-C_6 alkylamino, aminocarbonyl, C_1-C_6 alkylaminocarbonyl, C_1-C_6 alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, C_1-C_6 alkylaminosulfonyl, C_1-C_6 alkylsulfonyl, and heterocyclosulfonyl; more preferably hydrogen, alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, alkylthio, alkylamino, and aminocarbonyl. Most preferably R'_2 is hydrogen or aminocarbonyl.

Preferably, R'_5, R'_6, R'_9, and R'_{10} are independently selected from the group consisting of hydrogen, halo, halo(C_1-C_6)alkyl, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, nitro, amino, C_1-C_6 acylamino, amide, hydroxy, thiol, C_1-C_6 acyloxy, C_1-C_6 alkoxy, carboxy, carbonylamido and C_1-C_6 alkylthiol.

When Het^3 is $(i)^3$, $(ii)^3$ or $(vi)^3$, R'_2 is preferably attached to a carbon atom adjacent to a nitrogen atom.

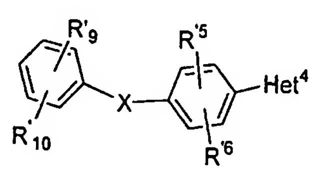
Preferably, Het^3 is selected from the group consisting of $(i)^3$, $(ii)^3$, $(iii)^3$, $(iv)^3$ and $(v)^3$.

One group of preferable compounds of Formula *III* include compounds wherein Het^3 is $(i)^3$ or $(ii)^3$; R'_1 is $C(O)R_{14}$; R'_2 is as defined above; R'_5, R'_6, and R'_{10}

are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; R'_9 is selected from the group consisting of halo, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; and $R_{14\text{-}16}$ and X are as defined above.

Another group of preferable compounds of Formula *III* include compounds wherein Het^3 is $(iii)^3$, $(iv)^3$, $(v)^3$ or $(vi)^3$; R'_1 is selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14}; R'_2 is as defined above; R'_5, R'_6, and R'_{10} are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; R'_9 is selected from the group consisting of halo, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; and $R_{14\text{-}16}$ and X are as defined above.

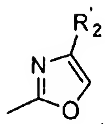
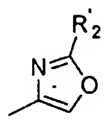
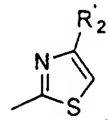
Further another group of useful compounds of the invention are those having the Formula *IV*:

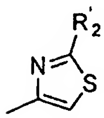


IV

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

Het^4 is selected from the group consisting of


(vii)^4 ;

(viii)^4 ;

(ix)^4 and


(x)^4 ;

R'_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cyano, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl;

R'_5, R'_6, R'_9, and R'_{10} are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$ where R_{15} is defined as above.

Het^4 is preferably selected from the group consisting of (vii)^4 and (x)^4. Preferably, R'_2, R'_5, R'_6, R'_9, and R'_{10} are as described for Formula ***III***.

Exemplary preferred compounds that may be employed in this method of invention include, without limitation:

3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

5-methylthio-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide;

5-methylsulfinyl-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide;

3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-methoxyphenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-aminophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(3-chloro-2-cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(2,4-difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-chloro-2-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(2-chloro-4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

1-[3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazolyl]ethanone;

2-methyl-1-[3-(4-phenoxyphenyl)-1H-pyrazole]propanone;

1-methanesulfonyl-3-(4-phenoxy)phenyl-1H-pyrazole;

2-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-1-(4-methyl)piperazin-1-yl-ethanone;

1-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-2-methyl-propan-2-ol;

1-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-propan-2-one;

1-morpholin-4-yl-2-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-ethanone;

1-[2-(methanesulfonylamino)ethyl]-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

1-(2-carbamoyloxyethyl)-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

3-[4-(4-fluorophenylthio)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-fluorophenylthio)phenyl]-1H-pyrazole;

2-[5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl]ethanol;

3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxylic acid dimethylamide;

1-benzyl-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

2-[3-[4-(4-fluorophenoxy)phenyl]-2H-pyrazol-2-yl]-1-pyrrolidin-1-yl ethanone;

2-(*N*-methylacetamido)-3-[4-(4-fluorophenoxy)phenyl]-2H-pyrazole;

2-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-acetamide;

2-{3-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-acetamide;

3-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-propionamide;

3-[3-fluoro-4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

2-{3-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-pyrimidine; and

2-{3-[4-(4-trifluoromethylphenoxy)phenyl]pyrazol-1-yl}pyrimidine.

Additional useful compounds of the present invention include:

4-[4-(4-fluorophenoxy)phenyl]-1H-imidazole;

4-[4-(4-fluorophenoxy)-3-fluorophenyl]-1H-imidazole;

4-[4-(4-fluorophenoxy)-3-fluorophenyl]-1H-imidazole, hydrochloride salt;

4-[4-(2,4-difluorophenoxy)phenyl]-1H-imidazole;

4-[4-(2,4-difluorophenoxy)phenyl]-1H-imidazole, hydrochloride salt;

4-[4-(2-fluoro-4-chlorophenoxy)phenyl]-1H-imidazole, hydrochloride salt;

4-(4-(4-trifluoromethylphenoxy)phenyl]-1H-imidazole, hydrochloride salt;

4-[4-(2,4-difluorophenoxy)phenyl]-2-methyl-1H-imidazole;

4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole-2-carboxamide;

2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole, hydrochloride salt;

2-[4-(4-fluorophenoxy)phenyl]-1H-benzimidazole;

2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole-4-carboxamide;

2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole-4-carbonitrile;

5-[4-(4-fluorophenoxy)phenyl]-pyrrole-2-carboxamide;

5-(4-phenoxyphenyl)pyrrole-2-carboxamide;

methyl 5-[4-(4-fluorophenoxy)phenyl]pyrrole-2-carboxylate;

2-[4-(4-fluorophenoxy)phenyl]oxazole-4-carboxamide; and

4-[4-(4-fluorophenoxy)-3-fluorophenyl]thiazole-2-carboxamide.

Useful aryl groups are C_{6-14} aryl, especially C_{6-10} aryl. Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.

Useful cycloalkyl groups are C_{3-8} cycloalkyl. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl,

benzofuryl, pyranyl, isobenzofuranyl, benzoxazonyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, and phenoxazinyl groups).

Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

Useful alkyl groups include straight-chained and branched C_{1-10} alkyl groups, more preferably C_{1-6} alkyl groups. Typical C_{1-10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, 3-pentyl, hexyl and octyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on the benzene ring of the compounds of the invention.

Useful alkenyl groups are C_{2-6} alkenyl groups, preferably C_{2-4} alkenyl. Typical C_{2-4} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec*-butenyl.

Useful alkynyl groups are C_{2-6} alkynyl groups, preferably C_{2-4} alkynyl. Typical C_{2-4} alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

Useful arylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned C_{6-14} aryl groups. Useful values include benzyl, phenethyl and naphthylmethyl.

Useful arylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Useful arylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned C_{6-14} aryl groups. Useful values include phenylethynyl and phenylpropynyl.

Useful heteroarylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful heteroarylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful heteroarylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned heteroaryl groups.

Useful cycloalkylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned cycloalkyl groups.

Useful haloalkyl groups include C_{1-10} alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g. fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

Useful hydroxyalkyl groups include C_{1-10} alkyl groups substituted by hydroxy, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

Useful alkoxy groups include oxygen substituted by one of the C_{1-10} alkyl groups mentioned above.

Useful alkylthio groups include sulfur substituted by one of the C_{1-10} alkyl groups mentioned above.

Useful acylamino groups are any C_{1-6} acyl (alkanoyl) attached to an amino nitrogen, e.g. acetamido, propionamido, butanoylamido, pentanoylamido, hexanoylamido as well as aryl-substituted C_{2-6} substituted acyl groups.

Useful acyloxy groups are any C_{1-6} acyl (alkanoyl) attached to an oxy (-O-) group, e.g. acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

The term heterocycle is used herein to mean saturated or partially unsaturated 3-7 membered monocyclic, or 7-10 membered bicyclic ring system, which consists of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples include, but are not limited to, pyrrolidine, piperazine, morpholine, imidazoline, pyrazolidine, benzodiazepines and the like.

Useful heterocycloalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned heterocyclic groups.

Useful alkylamino and dialkylamino groups are —NHR_{17} and —$NR_{17}R_{18}$, wherein R_{17} and R_{18} are C_{1-10} alkyl groups.

Aminocarbonyl group is –$C(O)NH_2$.

Useful alkylaminocarbonyl groups are carbonyl groups substituted by –NHR_{17} and –$NR_{17}R_{18}$, wherein R_{17} and R_{18} are C_{1-10} alkyl groups as defined above.

Useful alkylcarbonyl groups are carbonyl groups substituted by any of the above-mentioned C_{1-10} alkyl groups.

Useful alkylthiol groups include any of the above-mentioned C_{1-10} alkyl groups substituted by a –SH group.

Useful alkylsulfinyl groups include any of the above-mentioned C_{1-10} alkyl groups attached to a sulfinyl (–SO–).

Useful alkylsulfonyl groups include any of the above-mentioned C_{1-10} alkyl groups attached to a sulfonyl (–SO_2–).

Useful alkylaminosulfonyl groups include –NHR_{17} and –$NR_{17}R_{18}$ groups attached to a sulfonyl, wherein R_{17} and R_{18} are C_{1-10} alkyl groups as defined above.

Aminosulfonyl is –SO_2NH_2..

A carbamoyloxy group is –O–C(O) –NH_2.

A carboxy group is –COOH.

An azido group is –N_3.

An ureido group is –NH–C(O)–NH_2.

An amino group is –NH_2.

An amide group is an organic radical having –NHC(O)– as a functional group.

Optional substituents on R_1, R'_1 and R_{14}-R_{16} include any one of halo, halo(C_{1-6}) alkyl, aryl, heterocycle, cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, cycloalkyl(C_{1-6})alkyl, heterocyclo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, carboxy(C_{1-6})alkyl, alkoxy(C_{1-6})alkyl, nitro, amino, ureido, cyano, C_{1-6} acylamino, hydroxy, thiol, C_{1-6} acyloxy, azido, C_{1-6} alkoxy, carboxy, aminocarbonyl, carbamoyloxy, C_{1-6} alkylsulfonylamino, C_{1-6} acyl, and C_{1-6} alkylthiol groups mentioned above. Preferred optional substituents include: halo, halo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, hydroxy, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, aminocarbonyl, carbamoyloxy, C_{1-6} alkylsulfonylamino, C_{1-6} acyl and amino.

Unlike the semicarbazones disclosed by Dimmock *et al.* in U.S. Patent No. 5,741,818, which are somewhat flexible molecules, the pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles are much more rigid. In addition, the electronics of the pyrazole, imidazole, oxazole, thiazole and pyrrole ring are very different from that of a semicarbazone. For example, the 2'-nitrogen present in the semicarbazone is now replaced with the nitrogen atom at the 2-position of the pyrazole and thus is part of the six electron aromatic ring. Unlike the aminoalkanamides described by Pevarello, which contain a basic amine (pKa > 7), the heteroaryl compounds of the invention do not have to be basic. Pyrazole, for example, is half-protonated only at pH 2.5 and substitution with an electron withdrawing carbonyl is expected to reduce its basicity further. In addition, it was found that the primary amides present in the semicarbazones and the aminopropionamides are not necessary for activity as sodium channel blockers in the aryl-pyrazoles and -imidazoles claimed in the present application. Based on these considerations, it is an unexpected finding that the aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles and pyrroles show good activity as sodium channel blockers.

Since the compounds of Formula *I* are blockers of sodium (Na^+) channels, a number of diseases and conditions mediated by sodium ion influx can be treated employing these compounds. Therefore, the invention is related to a method of treating, preventing or ameliorating neuronal loss associated with stroke, global and focal ischemia, CNS trauma, hypoglycemia and surgery, spinal cord trauma; as well as treating or ameliorating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, treating or ameliorating anxiety, convulsions, glaucoma, migraine headache, and muscle spasm. The compounds of Formula *I* are also useful as antitinnitus agents, antimanic depressants, as local anesthetics, and as antiarrhythmics; as well as for treating, preventing or ameliorating pain including surgical, chronic and neuropathic pain. In each instance, the methods of the present invention require administering to an animal in need of such treatment an effective amount of a sodium channel blocker of the present invention, or a pharmaceutically acceptable salt or prodrug thereof.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable salts thereof of the disclosed compounds. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, secium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like.

The invention disclosed herein is also meant to encompass prodrugs of the disclosed compounds. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug *in vivo*.

The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

The invention disclosed herein is also meant to encompass the disclosed compounds being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Some of the compounds disclosed herein may contain one or more asymmetric centers and my thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

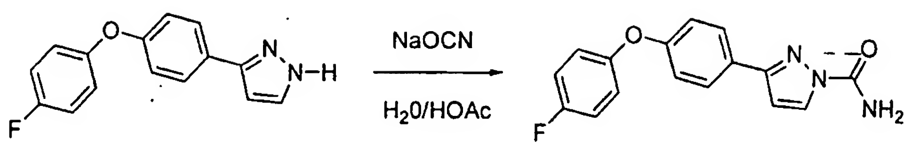
The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

The invention is also directed to a method for treating disorders responsive to the blockade of sodium channels in animals suffering thereof. Particular preferred embodiments of the aryl substituted heteroaryl compounds for use in method of this invention are represented by previously defined Formulae ***I-IV***.

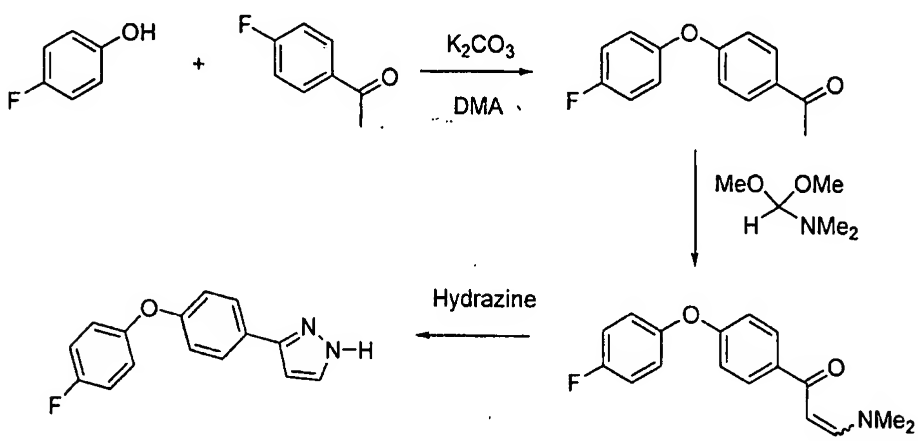
The compounds of this invention may be prepared using methods known to those skilled in the art. The 1H-pyrazoles of the present invention can be prepared as illustrated by exemplary reactions in Scheme 1 and 2. Scheme 1 illustrates the formation of a pyrazole-1-carboxamide from the corresponding 3-substituted-1H-pyrazole using sodium cyanate:

Scheme 1



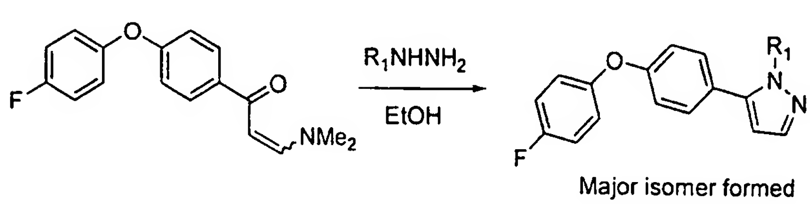
The 3-substituted-1H-pyrazoles were prepared as shown in Scheme 2 or were commerically available. 3-(4-Phenoxyphenyl)-1H-pyrazole, 3-[(4-nitrophenoxy)phenyl]-1H-pyrazole, 3-[(4-methoxyphenoxy)phenyl]-1H-pyrazole, 5-methylthio-3-(4-phenoxyphenyl)-1H-pyrazole and 3-[(3-chloro-2-cyanophenoxy)phenyl]-1H-pyrazole were obtained from Ryan Scientific (Isle of Palms, SC).

Scheme 2



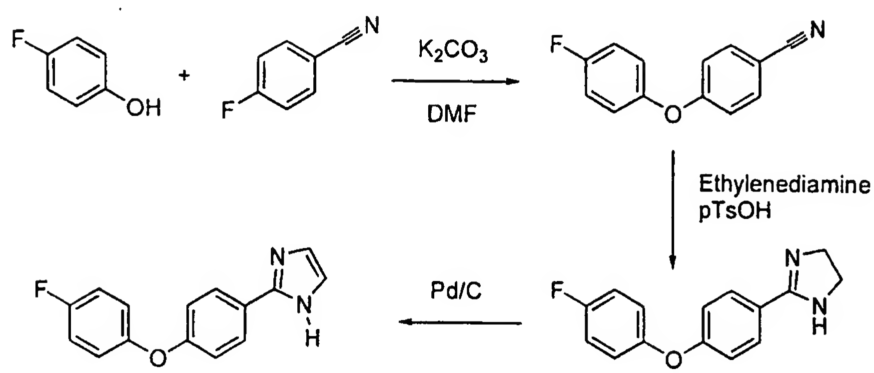
The 1,5-disubstituted pyrazoles can be prepared as shown in Scheme 3.

Scheme 3



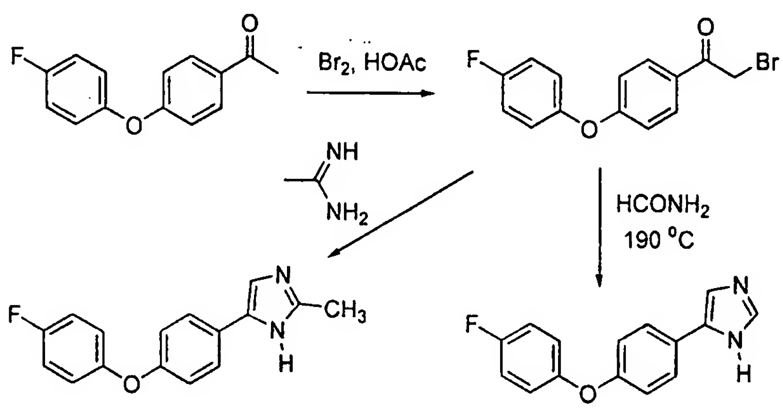
Compounds with Formula *I* wherein Het is (iii) can be prepared as illustrated by exemplary reactions in Scheme 4.

Scheme 4



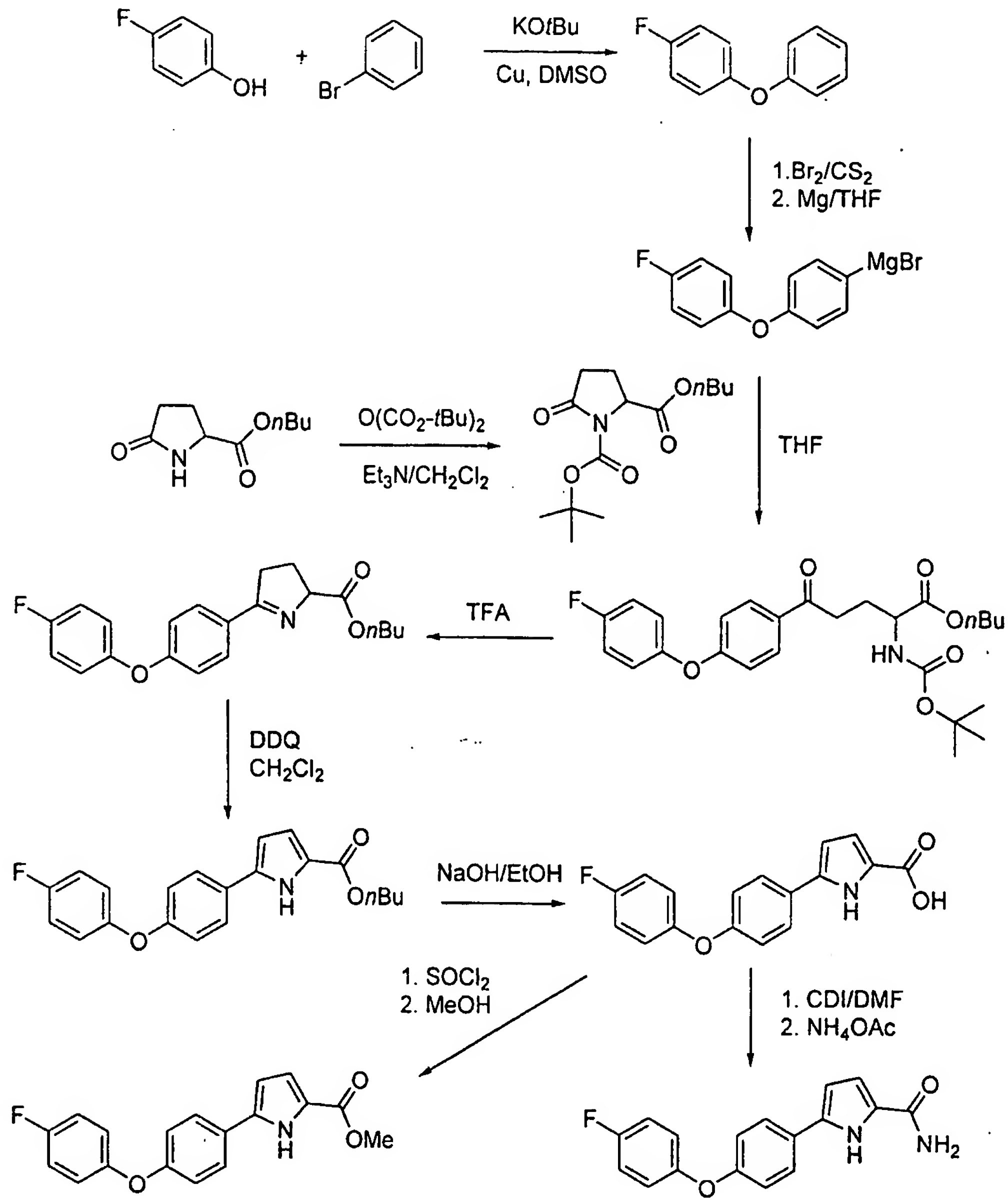
Compounds with Formula *I* where Het is (iv) and (v) can be prepared as illustrated by exemplary reactions in Scheme 5.

Scheme 5



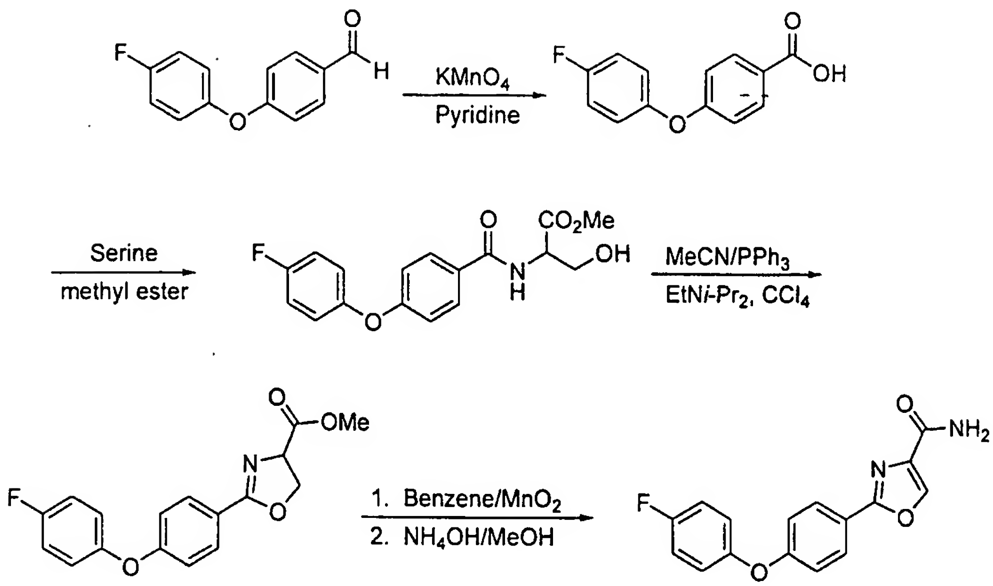
Compounds with Formula *I* where Het is (vi) can be prepared as illustrated by exemplary reactions in Scheme 6 using the method of Pichon, M. *et al.* (*Tetrahedron Lett. 37:* 7963-7966 (1966)) and Fournie-Zaluski, M-C. *et al.* (*J. Med. Chem. 39:* 2594-2608 (1996)).

Scheme 6



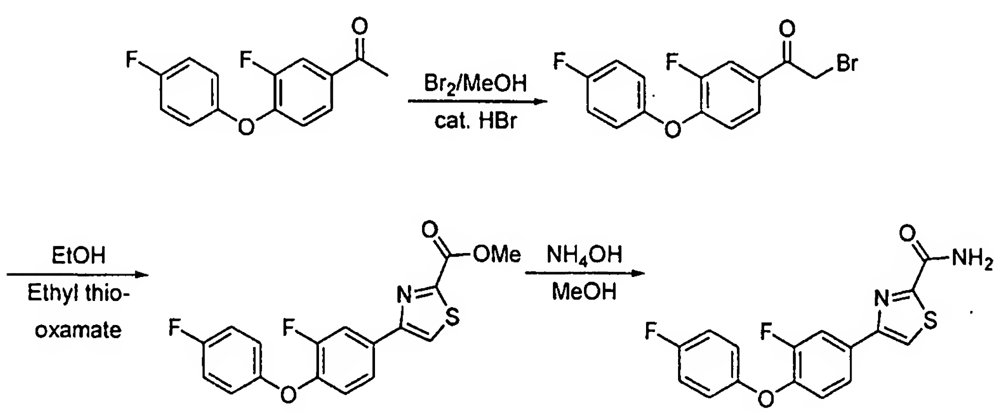
Compounds with Formula *I* wherein Het is (vii) can be prepared as illustrated in exemplary reactions in Sceme 7.

Scheme 7



Compounds with Formula *I* where Het is (x) can be prepared as illustrated by examplary reactions in Scheme 8.

Scheme 8



The invention is also directed to ^{3}H and ^{14}C radiolabeled compounds of Formula *I* and their use as radioligands for their binding site on the sodium channel. For example, one use of the labeled compounds of the invention is the characterization of specific receptor binding. Another use of the labeled compounds of

the invention is an alternative to animal testing for the evaluation of structure-activity relationships. The receptor assay is performed at a fixed concentration of a labeled compound of Formula *I* and at increasing concentrations of a test compound in a competition assay.

Tritiated compounds of Formula *I* can be prepared by introducing tritium into the compound of Formula *I* by, for example, catalytic dehalogenation with tritium. This method includes reacting a suitably halogen-substituted precursor of a compound of Formula *I* with tritium gas in the presence of a suitable catalyst, for example Pd/C, in the presence or absence of a base. Other suitable methods for preparing tritiated compounds can be found in Filer, *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A),* Chapter 6. ^{14}C-labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

The compounds of the present invention were assessed by electrophysiological assays in dissociated hippocampal neurons for sodium channel blocker activity. These compounds also could be assayed for binding to the neuronal voltage-dependent sodium channel using rat forebrain membranes and [^3H]BTX-B.

Sodium channels are large transmembrane proteins that are expressed in various tissues. They are voltage sensitive channels and are responsible for the rapid increase of Na^+ permeability in response to depolarization associated with the action potential in many excitable cells including muscle, nerve and cardiac cells.

One aspect of the present invention is the discovery of the mechanism of action of the compounds herein described as specific Na^+ channel blockers. Based upon the discovery of this mechanism, these compounds are contemplated to be useful in treating or preventing neuronal loss due to focal or global ischemia, and in treating or preventing neurodegenerative disorders including ALS, anxiety, and epilepsy. They are also expected to be effective in treating, preventing or ameliorating neuropathic pain, surgical pain, chronic pain and tinnitus. The compounds are also expected to be useful as antiarrhythmics, anesthetics and antimanic depressants.

The present invention is directed to compounds of Formulae *I-IV* that are blockers of voltage-sensitive sodium channels. According to the present invention, those compounds having preferred sodium channel blocking properties exhibit an IC_{50}

of about 100 μM or less in the electrophysiological assay described herein. Preferably, the compounds of the present invention exhibit an IC_{50} of 10 μM or less. Most preferably, the compounds of the present invention exhibit an IC_{50} of about 1.0 μM or less. Substituted heteroaryl compounds of the present invention may be tested for their Na^+ channel blocking activity by the following electrophysiological and binding assays.

Electrophysiological Assay 1:

Cell preparation: HEK-293 cells stably expressing the hSkM1 isoform of Na^+ channels (generous gift from Dr. A. L. George, Vanderbilt University Medical School) were cultured using standard techniques, as described previously (Verdoorn, T.A, *et al., Neuron 4*:919-928 (1990)). For electrophysiology, cells were plated onto 35 mm Petri dishes (pre-coated with poly-D-lysine) at a density of 1:40 on the day of re-seeding from confluent cultures. Our experience has been that cells are suitable for recordings for 2-3 days after plating.

Patch-clamp recordings of voltage-sensitive Na^+ currents: Whole-cell voltage-clamp recordings were made using conventional patch-clamp techniques (Hamill *et al., Pfluegers Arch. 391*:85-100 (1981)) with an Axopatch 200A amplifier (Axon Instruments, Foster City, CA). Recordings were made within 2-3 hours after neuron dissociation.The recording chamber was continuously superfused with the external solution (150 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, pH 7.4 (NaOH)) at a speed of about 1 mL/min. Recording pipettes were pulled from thick-walled capillaries (WPI, Sarasota, Fl) and fire-polished. The pipette resistances ranged from 1 to 3 MΩ when the pipettes were filled with internal solution containing (in mM): 110 CsF, 10 NaCl, 5 $MgCl_2$, 11 EGTA, 10 HEPES, pH adjusted to 7.4 with CsOH. Osmolality was set with a difference of 15-20 mmol/kg between external and internal solutions (lower inside the cell). Drugs and intervening wash-outs were applied through a linear array of flow pipes (Drummond Microcaps, 2 μL, 64-mm length). Compounds are dissolved in dimethylsulfoxide (DMSO) to make a 30 mM stock solution, which was subsequently

diluted into the external solution to give final concentrations of 0.1-100 μM. At the highest (1%) concentration, DMSO inhibited the size of Na^- current only slightly. Currents were recorded at room temperature (22-25°C), filtered at 5 kHz with an active 8-pole Bessel filter (Frequency Devices, Haverhill, MA), digitized at 10-50 μs intervals, and stored using Digidata 1200 analog/digital interface with Pclamp6/Clampex software (Axon Instruments). Series resistance was cancelled typically by ~75% when necessary. The inhibitory potency of drugs was assessed by measuring reductions in the peak amplitude of Na^+ currents induced by increasing concentrations of compounds tested. Na^+ currents were elicited by stepping membrane voltage from holding potentials over the range -100 mV to -50 mV, to a pulse potential of -10 mV. The test pulse duration was 5-10 msec, repeated at a frequency ≤ 1 Hz. Concentration-inhibition curves were fitted with equation 1:

$$I/I_{control} = 1/(1 + ([compound]/IC_{50})) \qquad \text{Eq. 1}$$

where $I_{control}$ is the maximal Na^+ current in the absence of antagonist, [compound] is the drug concentration, and IC_{50} is the concentration of compound that produces half maximal inhibition.

Electrophysiological Assay 2:

Cell preparation: HEK-293 (NaIIA-B2) cell line stably expressing the rBIIA isoform of Na^+ channels was established in-house. The cells were cultured using standard techniques, as described previously (Verdoorn, T.A, *et al., Neuron 4*:919-928 (1990)). For electrophysiology, cells were plated onto poly-D-lysine pre-coated Cellware 35 mm Petri dishes (BIOCOAT, Becton Dickinson) at a density of ~10^4 cells/dish on the day of re-seeding from confluent cultures. Our experience has been that cells are suitable for recordings for 2-3 days after plating.

Patch-clamp recordings of voltage-sensitive Na^+ currents: Whole-cell voltage-clamp recordings were made using conventional patch-clamp techniques (Hamill *et al., Pfluegers Arch. 391*:85-100 (1981)) with an Axopatch 200A amplifier

(Axon Instruments, Foster City, CA). The recording chamber was continuously superfused with the external solution (150 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, pH 7.4 adjusted with NaOH, osmolality ~320 mmol/kg) at a speed of about 1 mL/min. Recording pipettes were pulled from the thick-walled capillaries (WPI, Sarasota, Fl) and fire-polished. The pipette resistances ranged from 1 to 3 MΩ when the pipettes were filled with internal solution containing (in mM): 130 CsF, 20 NaCl, 2 $MgCl_2$, 10 EGTA, 10 HEPES, pH adjusted to 7.4 with CsOH, osmolality ~310 mmol/kg. Drugs and intervening wash-outs were applied through a linear array of flow pipes (Drummond Microcaps, 2 μL, 64-mm length). Compounds are dissolved in dimethylsulfoxide (DMSO) to make a 30 mM stock solution, which was subsequently diluted into the external solution to give final concentrations of 0.1-100 μM. At the highest (1 %) concentration, DMSO inhibited the size of Na^+ current only slightly. Currents were recorded at room temperature (22-25 °C), filtered at 3 kHz with an active 8-pole Bessel filter (Frequency Devices, Haverhill, MA), digitized at 10-50 μs intervals, and stored using Digidata 1200 analog/digital interface with Pclamp6/Clampex software (Axon Instruments). Series resistance was cancelled typically by ~75% when necessary.

The following voltage pulse protocols were used to assess the potency and kinetics of inhibition of the Na^+ channels by the compounds (Fig. 1).

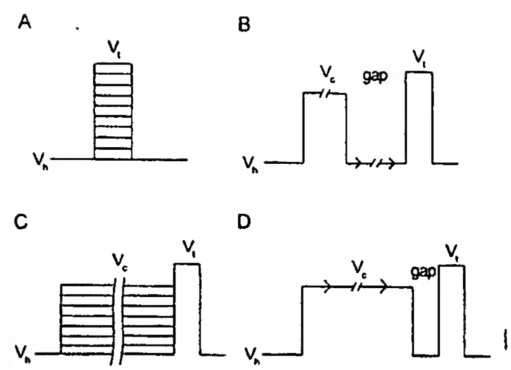


Figure 1. Voltage pulse protocols. **A.** IV-curves. **C.** Steady-state inactivation. **B.** Repriming kinetics. **D.** Time course of binding.

Current-voltage relationship (IV-curve), protocol **A**, was used to report the voltage at which the maximal inward Na^+ current is achieved. This voltage was used throughout the experiment as testing voltage, V_t. The steady-state inactivation (or, availability) curve, protocol **C**, was used to get the voltage at which almost complete ($\geq$95%) inactivation of Na^+ channels occurs; it served as voltage for conditioning prepulse, V_c, throughout the experiment. Protocol **B** reports how fast the channels recover from inactivation at hyperpolarized voltages. This permitted us to set up the duration of the hyperpolarization gap which is used in measurement of the kinetics of binding of compounds to inactivated Na^+ channels (protocol **D**). Channel repriming under control conditions was fast ($\geq$90% recovery during first 5-10 ms). If a drug substantially retards the repriming process then it becomes possible (protocol **D**) to accurately measure the kinetics of binding of the inhibitor to inactivated channels as well as the steady-state affinity (k_+ and K_i). To estimate k_+ values the reduction in peak currents in successive trials with varying pre-pulse duration was plotted as a function of pre-pulse duration and the time constant (τ) measured by mono-exponential fit. A plot of $1/\tau$ as a function of antagonist concentration then allowed calculating of the macroscopic binding rates of the antagonists. To determine K_i values the partial inhibition curves measured by fractional responses in steady-state were fitted with the logistic equation:

$$I/I_{control} = 1/(1 + ([antagonist]/K_i)^p), \qquad \text{Eq. 2}$$

where $I_{control}$ is the maximal Na^+ current in the absence of antagonist, [antagonist] is the drug concentration, K_i is the concentration of antagonist that produces half maximal inhibition, and p is the slope factor.

In vitro Binding Assay:

The ability of compounds of the present invention to modulate either site 1 or site 2 of the Na^+ channel was determined following the procedures fully described in Yasushi, *J. Biol. Chem. 261*:6149-6152 (1986) and Creveling, *Mol. Pharmacol. 23*:350-358 (1983), respectively. Rat forebrain membranes were used as sources of Na^- channel proteins. The binding assays were conducted in 130 μM choline chloride at 37°C for 60-minute incubation with $[^3H]$ saxitoxin and $[^3H]$ batrachotoxin as radioligands for site 1 and site 2, respectively.

In vivo Pharmacology:

The compounds of the present invention may be tested for *in vivo* anticonvulsant activity after i.v., p.o. or i.p. injection using a number of anticonvulsant tests in mice, including the maximum electroshock seizure test (MES). Maximum electroshock seizures were induced in male NSA mice weighing between 15-20 g and male Sprague-Dawley rats weighing between 200-225 g by application of current (50 mA, 60 pulses/sec, 0.8 msec pulse width, 1 sec duration, D.C., mice; 99 mA, 125 pulses/sec, 0.8 msec pulse width, 2 sec duration, D.C., rats) using a Ugo Basile ECT device (Model 7801). Mice were restrained by gripping the loose skin on their dorsal surface and saline-coated corneal electrodes were held lightly against the two corneae. Rats were allowed free movement on the bench top and ear-clip electrodes were used. Current was applied and animals were observed for a period of up to 30 seconds for the occurrence of a tonic hindlimb extensor response. A tonic seizure was defined as a hindlimb extension in excess of 90 degrees from the plane of the body. Results were treated in a quantal manner.

The compounds may be tested for their antinociceptive activity in the formalin model as described in Hunskaar, S., O. B. Fasmer, and K. Hole. *J. Neurosci. Methods 14:* 69-76 (1985). Male Swiss Webster NIH mice (20-30 g; Harlan, San Diego, CA) were used in all experiments. Food was withdrawn on the day of experiment. Mice were placed in Plexiglass jars for at least 1 hour to accommodate to the environment. Following the accommodation period mice were weighed and given either the compound of interest administered i.p. or p.o., or the appropriate volume of vehicle (10 % Tween-80). Fifteen minutes after the i.p. dosing, and 30 minutes after the p.o. dosing mice were injected with formalin (20 μL of 5% formaldehyde solution in saline) into the dorsal surface of the right hind paw. Mice were transferred to the Plexiglass jars and monitored for the amount of time spent licking or biting the injected paw. Periods of licking and biting were recorded in 5 minute intervals for 1 hour after the formalin injection. All experiments were done in a blinded manner during the light cycle. The early phase of the formalin response was measured as licking / biting between 0-5 min, and the late phase was measured from 15-50 min. Differences between vehicle and drug treated groups were analyzed by one-way analysis of variance (ANOVA). A P value $\leq$0.05 was considered significant. Having activity in blocking the acute and second phase of formalin-induced paw-licking activity, the compounds are considered to be efficacious for acute and chronic pain.

The compounds may be tested for their potential for the treatment of chronic pain (antiallodynic and antihyperalgesic activities) in the Chung model of peripheral neuropathy. Male Sprague-Dawley rats weighing between 200-225 g were anesthetized with halothane (1-3 % in a mixture of 70 % air and 30 % oxygen) and their body temperature controlled during anesthesia through use of a homeothermic blanket. A 2-cm dorsal midline incision was then made at the L5 and L6 level and the para-vertibral muscle groups retracted bilaterally. L5 and L6 spinal nerves were then be exposed, isolated, and tightly ligated with 6-0 silk suture. A sham operation was performed exposing the contralateral L5 and L6 spinal nerves as a negative control.

Tactile Allodynia: Rats were transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A series of Semmes-Weinstein monofilaments were applied to the plantar surface of the hindpaw to

determine the animal's withdrawal threshold. The first filament used possessed a buckling weight of 9.1 gms (.96 log value) and was applied up to five times to see if it elicited a withdrawal response. If the animal had a withdrawal response then the next lightest filament in the series would be applied up to five times to determine if it could elicit a response. This procedure was repeated with subsequent lesser filaments until there was no response and the lightest filament that elicited a response was recorded. If the animal did not have a withdrawal response from the initial 9.1 gms filament then subsequent filaments of increased weight were applied until a filament elicited a response and this filament was then recorded. For each animal, three measurements were made at every time point to produce an average withdrawal threshold determination. Tests were performed prior to and at 1, 2, 4 and 24 hours post drug administration. Tactile allodynia and mechanical hyperalgesia tests were conducted concurrently.

Mechanical Hyperalgesia: Rats were transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A slightly blunted needle was touched to the plantar surface of the hindpaw causing a dimpling of the skin without penetrating the skin. Administration of the needle to control paws typically produced a quick flinching reaction, too short to be timed with a stopwatch and arbitrarily given a withdrawal time of 0.5 sec. The operated side paw of neuropathic animals exhibited an exaggerated withdrawal response to the blunted needle. A maximum withdrawal time of ten seconds was used as a cutoff time. Withdrawal times for both paws of the animals were measured three times at each time point with a five-minute recovery period between applications. The three measures were used to generate an average withdrawal time for each time point. Tactile allodynia and mechanical hyperalgesia tests were conducted concurrently.

The compounds may be tested for their neuroprotective activity after focal and global ischemia produced in rats or gerbils according to the procedures described in Buchan *et al.* (*Stroke*, Suppl. 148-152 (1993)) and Sheardown *et al.* (*Eur. J. Pharmacol. 236*:347-353 (1993)) and Graham *et al.* (*J. Pharmacol. Exp. Therap. 276*:1-4 (1996)).

The compounds may be tested for their neuroprotective activity after traumatic spinal cord injury according to the procedures described in Wrathall *et. al.* (*Exp. Neurology 137*:119-126 (1996)) and Iwasaki *et. al.* (*J. Neuro Sci. 134*:21-25 (1995)).

Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount that is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for epilepsy, neurodegenerative diseases, anesthetic, arrhythmia, manic depression, and pain. For intramuscular injection, the dose is generally about one-half of the oral dose.

In the method of treatment or prevention of neuronal loss in global and focal ischemia, brain and spinal cord trauma, hypoxia, hypoglycemia, status epilepsy and surgery, the compound can be administrated by intravenous injection at a dose of about 0.025 to about 10 mg/kg.

The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the particular heteroaryl compound of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, and the like. Basic salts are formed by mixing a solution of the heteroaryl compound of the present invention with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The pharmaceutical compositions of the invention may be administered to any animal that may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well

as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropymethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations, which can be used rectally, include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active

compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, and include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

Example 1

3-[4-(4-Fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide

a) **1-[4-(4-Fluorophenoxy)phenyl]ethanone:** A mixture of 4'-fluoroacetophenone (2.2 mL, 17.9 mmol), 4-fluorophenol (2.34 g, 20.6 mmol), and potassium carbonate (5.2 g, 38 mmol) in DMF (17 mL) was refluxed for 16 hours. The mixture was diluted with ethyl acetate and washed several times with an aqueous sodium hydroxide solution (2 N). The organic layer was separated, dried over sodium sulfate, filtered, and evaporated under reduced pressure to give 1-[4-(4-fluorophenoxy)phenyl]ethanone. ^1H NMR ($CDCl_3$): δ 7.93 (d, J = 8.7 Hz, 2H), 7.09-7.04 (m, 4H), 6.96 (d, J = 8.4 Hz, 2H), 2.57 (s, 3H).

b) **3-[4-(4-Fluorophenoxy)phenyl]-1H-pyrazole.** A mixture of crude 1-[4-(4-fluorophenoxy)phenyl]ethanone (17.9 mmol) and *N*,*N*-dimethylformamide dimethylacetal (2.6 mL, 18.4 mmol) in DMF (20 mL) was refluxed for 24 hours. The solution was then partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate and the combined ethyl acetate layers were washed twice with water, dried over sodium sulfate, filtered, and evaporated under reduce pressure to give a yellow solid. The solid was dissolved in ethanol and neat hydrazine hydrate (2.2 mL, 70 mmol) was added. The solution was refluxed for 6 hours. After cooling to room temperature, the reaction was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined ethyl acetate layers were washed several times with water, dried over sodium sulfate, and evaporated under reduced pressure to give 4.4 g (97% crude yield) of 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole. ^{1}H NMR ($CDCl_3$): δ 10.6 (bs, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 2.1 Hz, 1H), 7.04-6.99 (m, 6H), 6.57 (d, J = 2.4 Hz, 1H).

c) **3-[4-(4-Fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide.** A solution of crude 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole (4.4 g, 17.3 mmol) in glacial acetic acid (60 mL) and water (5 mL) was treated with a solution of sodium cyanate (1.4 g, 21 mmol) in 5 mL of water. After stirring at room temperature for 16 hours, the reaction was diluted with water, giving a solid precipitate. The crude product was filtered, dried and purified by column chromatography to give 2.79 g (52%) of the title compound as solid, mp 141-143 °C. ^{1}H NMR (DMSO-d_6): δ 8.28 (d, J = 3.0 Hz, 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.84 (bs, 2H), 7.24 (t, J = 8.4 Hz, 2H), 7.13-7.08 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 2.7 Hz, 1H).

The following pyrazole-1-carboxamides were prepared by using a similar procedure:

3-[4-(2,4-Difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide; mp132-134 °C. ^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 2.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.15-7.08 (m, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.94-6.85 (m, 1H), 6.67 (d, J = 3.0 Hz, 1H), 5.30 (bs. 2H).

3-[4-(4-Chloro-2-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide; mp 150-151 °C. ^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 10.0 Hz, 1H), 7.13 (d, J = 9.6 Hz, 1H), 7.06 (d, J = 8.4 Hz,1H), 7.02 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 3.0 Hz, 1H), 5.25 (bs, 2H).

3-[4-(4-Trifluoromethylphenoxy)phenyl]-1H-pyrazole-1-carboxamide; mp 131-132 °C. ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H, J = 2.7 Hz), 7.86 (d, 2H, J = 8.4 Hz), 7.59 (d, 2H, J = 8.4 Hz), 7.16 (br s, 1H), 7.11 (d, 2H, J = 8.4 Hz), 7.09 (d, 2H, J = 8.4 Hz), 6.71 (d, 1H, J = 2.7 Hz), 5.81 (br s, 1H). The compound was prepared from 3-[4-(4-trifluoromethylphenoxy)phenyl]-1H-pyrazole, mp 102-104 °C, R_f 0.33 (7/3 hexane/EtOAc), which in turn was prepared from 1-[4-(4-trifluoromethylphenoxy)phenyl]ethanone using the procedure described for the synthesis of 3-[4-(4-fluoromethylphenoxy)phenyl]-1H-pyrazole.

3-[4-(2-chloro-4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide can also be prepared by a similar method.

The following 3-substituted-pyrazole-1-carboxamides were prepared from the commercially available 3-substituted-1H-pyrazoles (Ryan Scientific, Isle of Palms, SC) as described for the conversion of 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole to 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide:

3-[4-(4-Methoxyphenoxy)phenyl]-1H-pyrazole-1-carboxamide; mp 156-159 °C; ^{1}H NMR ($CDCl_3$): δ 8.23 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.14 (bs, 1H), 7.00 (dd, J = 9.0, 7.8 Hz, 4H), 6.90 (d, J = 9.3 Hz, 2H), 6.67 (d, J = 2.4 Hz, 1H), 5.25 (bs, 1H), 8.32 (s, 3H).

5-Methylthio-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide; mp 142-144 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 8.7 Hz, 2H), 7.37 (t, J = 8.4 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.07-7.04 (m, 4H), 6.34 (s, 1H), 5.20 (bs, 2H), 2.53 (s, 3H).

3-[4-(4-Nitrophenoxy)phenyl]-1H-pyrazole-1-carboxamide; mp 145-147 °C; ^{1}H NMR ($CDCl_3$): δ 8.28 (d, J = 2.4 Hz, 1H), 8.23 (d, J = 9.0 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 9.3 Hz, 2H), 6.73 (d, J = 3.0 Hz, 1H), 5.3 (bs, 2H).

3-[4-(3-Chloro-2-cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide; mp 180-181 °C; ^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 3.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 3.0 Hz, 1H), 5.27 (bs, 2H).

Example 2

5-Methanesulfinyl-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide

To a solution of 5-thiomethyl-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide (122 mg, 0.375 mmol) in $CHCl_3$ at 0 °C was added solid m-chloroperoxybenzoic acid (57-86%; 129 mg). After several hours at 0 °C, solid $Na_2S_2O_3$ was added and the mixture was stirred overnight. The reaction was added to a water/EtOAc mixture. The aqueous layer was washed with EtOAc and the pooled EtOAc layers were dried (Na_2SO_4), filtered, and concentrated to dryness. Column chromatography (1:1 hexane/EtOAc) gave 74 mg (58%) of the sulfoxide as a white solid, mp 92 °C. ^{1}H NMR ($CDCl_3$): δ 7.79 (d, 2H, J = 8.7 Hz), 7.38 (t, 2 H, J = 8.0 Hz), 7.29 (s, 1H), 7.14 (t, 1H, J = 7.2 Hz), 7.06 (d, 4H, J = 8.4 Hz), 5.45 (br s, 2H), 3.05 (s, 3H).

Example 3

3-[4-(4-Aminophenoxy)phenyl]-1H-pyrazole-1-carboxamide

A solution of 3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole-1-carboxamide (100 mg, 0.308 mmol) in ethanol was flushed with nitrogen for 5 min, then palladium (10% on carbon, 20 mg) was added. The mixture was shaken under 40 psi of hydrogen for 16 hours. The mixture was then filtered through a bed of Celite and the solvent was removed in vacuo. The crude product was purified by column chromatography to give 57 mg (60%) of the title compound as a solid, mp 158-160 °C. ^{1}H NMR ($CDCl_3$): δ 8.22 (d, J = 3.0 Hz, 1H), 7.75 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 7.10 (bs, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 3.0 Hz, 1H), 5.25 (bs. 1H), 3.61 (bs, 2H).

Example 4

3-[4-(2-Cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide

A solution of 3-[4-(3-chloro-2-cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide (65 mg, 0.192 mmol) in ethanol formed upon heating. The solution was allowed to cool to room temperature, purged with nitrogen for 5 minutes, and 10% palladium on carbon (25 mg) was added. The mixture was stirred for 16 hours under a balloon filled with hydrogen. The mixture was then filtered through a bed of Celite and the filtrate was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the crude product. Purification by column chromatography (60:40 hexane/ethyl acetate) afforded 15 mg (26%) of the title compound as a solid. TLC R_f = 0.38 (60:40 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 8.26 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.69 (dd, J = 7.5, 1.5 Hz, 1H), 7.53-7.47 (m, 1H), 7.20-7.14 (m, 1H), 7.15 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 8.7 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 5.30 (bs, 2H).

Example 5

1-[3-[4-(4-Nitrophenoxy)phenyl]-1H-pyrazolyl]ethanone

A solution of 3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole (0.16 g, 0.57 mmol) in pyridine (12 mL) was treated with neat acetic anhydride (1.0 mL, 1.0 mmol) and allowed to stir at room temperature for 16 hours. The reaction was then diluted with ethyl acetate, washed several times with an aqueous 2N HCl solution, dried over sodium sulfate, and evaporated under reduced pressure. The crude product was purified by column chromatography, affording 116 mg (63%) of the title compound. TLC R_f 0.78 (70:30 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 3.0 Hz, 1H). 8.22 (d, J = 9.3 Hz, 2H), 7.94 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.3 Hz, 2H), 6.77 (d, J = 3.0 Hz, 1H), 2.78 (s, 3H).

Example 6

2-Methyl-1-[3-(4-phenoxyphenyl)-1H-pyrazol-1-yl]-propan-1-one

A mixture of 3-(4-phenoxyphenyl)-1H-pyrazole (123 mg, 0.52 mmol) and NaH (28 mg, 0.70 mmol) in 5 mL of DMF was stirred at room temperature for 30 minutes. Neat isobutyryl chloride (80 μL, 0.75 mmol) was added and the reaction was stirred at room temperature. The reaction was then partitioned between water and EtOAc. The aqueous layer was extracted twice with EtOAc and the pooled organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Column chromatography (5% EtOAc/hexane) gave 127 mg (80%) of the title compound as a white solid, mp 49-51 °C. ^{1}H NMR ($CDCl_3$): δ 8.30 (d, J=3.0 Hz, 1H), 7.88 (d, J=8.7 Hz, 2H), 7.39 (t, J=8.0 Hz, 2H), 7.17 (t, J=7.2 Hz, 2H), 7.12-7.08 (m, 4H), 6.75 (d, J=3.0 Hz, 1H), 4.03 (m, 1H), 1.78 (d, J=6.9 Hz, 6H).

Example 7

1-Methanesulfonyl-3-(4-phenoxyphenyl)-1H-pyrazole

To a solution of 3-(4-phenoxyphenyl)-1H-pyrazole (125 mg, 0.529 mmol) in pyridine (10 mL) at room temperature was added neat methanesulfonyl chloride (50 μL, 0.64 mmol). After stirring overnight at room temperature, the reaction was diluted with water. Column chromatography afforded 152 mg (91%) of the title compound as white solid, mp 136 °C. ^{1}H NMR ($CDCl_3$): δ 8.06 (d, J = 3.0 Hz, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.37 (t, J = 8.7 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 7.06-7.04 (m, 2H), 6.72 (d, J = 3.0 Hz, 1H), 3.38 (s, 3H).

Example 8

1-[2-(Methanesulfonylamino)ethyl]-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole

a) **2-[2-[5-[4-(4-Fluorophenoxy)phenyl]pyrazol-1-yl]ethyl]-isoindole-1,3-dione.** A solution of 2-[5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl]ethanol (210 mg, 0.704 mmol), triphenylphosphine (249 mg, 0.949 mmol) and phthalimide (149 mg,

1.01 mmol) in 5 mL of dry THF was cooled in an ice-water bath and neat diethyl azodicarboxylate (145 μL, 160 mg, 0.919 mmol) was added dropwise via syringe. The resulting yellow solution was stirred at room temperature overnight. TLC (9:1 CH_2Cl_2/EtOAc) indicated the reaction was not complete and it was allowed to stir at room temperature for an additional 24 hours. The reaction was then cooled in an ice-water bath and quenched with a brine solution. Water was added and the aqueous layer was separated and washed with EtOAc (3 x 5 mL). The pooled organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was dissolved in 1:1 EtOAc/hexane with a minimum of CH_2Cl_2 added to give a clear solution. The resulting solution was added to 11 cm of flash silica gel in a 4 cm diameter column. Elution with 1:1 EtOAc/hexane afforded 218 mg of the desired product contaminated with 1,2-bis(ethoxycarbonyl)hydrazine. Column chromatography (silica gel, 9:1 CH_2Cl_2/EtOAc) afforded 196 mg (65%) of pure product, mp 126-127 °C. ^{1}H NMR ($CDCl_3$): δ 7.76-7.64 (m, 4H), 7.48 (d, 1H, J = 2 Hz), 7.17 (d, 2H, J = 8 Hz), 7.10-6.99 (m, 4H), 6.82 (d, 2H, J = 8 Hz), 6.20 (d, 1H, J = 2 Hz), 4.49 (t, 2H, J = 7 Hz), 3.96 (t, 2H, J = 7 Hz).

b) 1-[2-(Methanesulfonylamino)ethyl]-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole. A suspension of 2-[2-[5-[4-(4-fluorophenoxy)phenyl]pyrazol-1-yl]ethyl]-isoindole-1,3-dione (126 mg, 0.295 mmol) in 3 mL of a 2M solution of $MeNH_2$ in MeOH was stirred at room temperature for 48 hours. The reaction was then conc. to dryness. Column chromatography (34 cm of flash silica gel in a 2 cm dia. column; eluted with 9:1 $CHCl_3$/MeOH) afforded 36 mg of the desired amine. A solution of this amine (34 mg, 0.12 mmol) in 1 mL of pyridine was treated with neat methanesulfonyl chloride (22 μL, 32 mg, 0.28 mmol) added via syringe. After stirring overnight, an additional 50 μL (74 mg, 0.65 mmol) of methanesulfonyl chloride was added dropwise via syringe. After stirring overnight, the reaction was diluted with EtOAc and extracted with an aqueous 1M HCl solution (1 x 15 mL and 1 x 5 mL). The aqueous layer was back extracted with EtOAc and the combined EtOAc layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The residue was added to 4.5 g of flash silica gel in a 1 cm diameter column. Elution

with 140 mL of 3:1 EtOAc/hexane afforded 43 mg (95%) of the title compound as a light yellow solid, mp 96-98 °C. [1]H NMR ($CDCl_3$): δ 7.53 (d, 1H, J = 2.1 Hz), 7.32 (d, 2H, J = 8.7 Hz), 7.10-7.05 (m, 4H), 7.25 (d, 2H, J = 9 Hz), 6.29 (d, 1H, J = 1.8 Hz), 5.45 (br t, 1H, J = 6 Hz), 4.26 (m, 2H), 3.59 (m, 2H), 2.89 (s, 3H).

Example 9

1-(2-Carbamoyloxyethyl)-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole

A solution of 2-[5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl]ethanol (118 mg, 0.40 mmol) in 1 mL of toluene was treated with solid sodium cyanate (2 eq.; 53 mg, 0.82 mmol) added in one portion. The resulting mixture was cooled in an ice-water bath and neat trifluoroacetic acid (60 μL, 89 mg, 0.78 mmol) was added dropwise via syringe. The reaction was stirred at room temperature. After 2 hours, the reaction had completely solidified and an additional 1 mL of toluene was added. After stirring overnight, the reaction was recooled to 0 °C and diluted with 3 mL of a saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated. Column chromatography (13 cm of flash silica in a 2 cm diameter column eluted with 600 mL of 3:2 CH_2Cl_2/EtOAc) afforded 21 mg (15 %) of the carbamate as a solid, mp 120-125 °C. [1]H NMR ($CDCl_3$): δ 7.57 (d, 1H, J = 2 Hz), 7.35 (d, 2H, J = 9 Hz), 7.10-7.05 (m, 4H), 7.02 (d, 2H, J = 9 Hz), 6.26 (d, 1H, J = 2 Hz), 4.60 (br s, 2H), 4.43 (t, 2H), 4.35 (t, 2H).

Example 10

3-[4-(4-Fluorophenylthio)phenyl]-1H-pyrazole

a) **4-Acetyl-4'-fluoro-diphenyl thioether.** A mixture of 4'-fluoroacetophenone (0.98 g, 7.1 mmol), 4-fluorothiophenol (1.0 g, 7.8 mmol) and K_2CO_3 (0.88 g, 6.4 mmol) was heated in 50 mL *N,N*-dimethylacetamide at 155 °C for 15 hours. After cooling to room temperature, the reaction was quenched with 50 mL of

water. Chloroform (2 x 50 mL) was used to extract the product. The combined organic layers were washed with an aqueous 2 N NaOH solution and brine, dried over Na_2SO_4 and evaporated. The oil that was obtained was dissolved in 300 mL of ether and washed four times with water to remove *N,N*-dimethylacetamide. The ethereal solution was dried over Na_2SO_4 and evaporated to give 1.9 g of 4-acetyl-4′-fluoro-diphenyl thioether as an oil.

b) **3-[4-(4-Fluorophenylthio)phenyl]-1H-pyrazole.** A solution of 4-acetyl-4′-fluoro-diphenyl thioether (0.75 g, 3.1 mmol) and *N,N*-dimethylformamide dimethylacetal (0.47 mL, 3.4 mmol) in 6 mL of DMF was heated at 155 °C overnight. Once at room temperature, the solution was poured into 30 mL of water. EtOAc (2 x 100 mL) was used to extract the product. The combined organic layers were washed with water three times, dried over Na_2SO_4 and evaporated to yield 0.85 g of a dark-brown oil. A solution of the oil in 6 mL of EtOH containing hydrazine-hydrate (0.47 mL, 15.3 mmol) was heated at reflux for 1.5 h. After cooling to room temperature, 30 mL of water was poured into the reaction mixture. EtOAc (2 x 75 mL) was used to extract the product. The organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated. The crude product was purified on a silica gel column, eluting with 40% EtOAc/hexane, to yield 0.65 g (79%) of the title compound as a yellow oil, TLC R_f = 0.45 (1:1 EtOAc/hexane). ^1H NMR (300 MHz, DMSO-d_6): δ 12.95 (s, 1H, NH), 7.83 (br s, 1H), 7.81, 7.44 and 7.29 (m, 8H, PhH), 6.72 (br s, 1H).

Example 11

3-[4-(4-Fluorophenylthio)phenyl]-1H-pyrazole-1-carboxamide

A solution of 3-[4-(4-fluorophenylthio)phenyl]-1*H*-pyrazole (85 mg, 0.31 mmol) in 1.5 mL glacial acetic acid was treated with a solution of sodium cyanate (31 mg. 0.47 mmol) in 0.5 mL of water. The resulting white suspension was stirred at room temperature overnight. The suspension was then diluted with 10 mL of EtOAc, resulting in a yellow solution which was washed with water and sat. $NaHCO_3$

solution, dried over Na_2SO_4 and evaporated. The residue was triturated with 3 mL of 25% EtOAc/hexane. The white solid that formed was collected by filtration and dried to give 65 mg (66%) of the title compound, mp 150-155 °C (TLC R_f = 0.22 (25% EtOAc/hexane)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 2.1 Hz, 1H, pyrazole H), 7.77 (d, J = 7.5 Hz, 2H, PhH), 7.48-7.06 (m, 6H, PhH), 6.71 (d, J = 2.1 Hz, 1H, pyrazole H), 5.31 (br s, 2H, NH_2).

Example 12

2-[5-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1-yl]ethanol

A solution of 3-dimethylamino-1-[4-(4-fluorophenoxy)phenyl]-propenone (1.00 g, 3.50 mmol) and 2-hydroxyethylhydrazine (307 mg, 4.03 mmol) in 8 mL of EtOH was heated at reflux for 2 hours. TLC indicated incomplete reaction and an additional 88 mg (1.12 mmol) of the hydrazine was added. After 3.5 hours at reflux, the reaction was allowed to cool and concentrated in vacuo. The residue was dissolved in EtOAc and added to 12.5 cm of flash silica gel in a 4 cm diameter column. Elution with 100% EtOAc afforded 920 mg (88%) of the product as a 10:1 mixture of 1,5- and 1,3-isomers. The mixture (900 mg) was suspended in 5 mL of pyridine, cooled in an ice-water bath and treated with neat acetic anhydride (355 μL, 384 mg, 3.76 mmol) added dropwise via syringe. The resulting clear solution was stirred at room temperature overnight. The reaction was cooled in an ice-water bath and added to 35 mL of an ice-cold aqueous 2N HCl solution and 30 mL of EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine. After drying (Na_2SO_4), the solvent was removed in vacuo. Column chromatography (12 cm of flash silica in a 4 cm diameter column, elution with 600 mL of 5% EtOAc/CH_2Cl_2 and 200 mL of 10%, 300 mL of 15 % and 100 mL each of 20 and 30% EtOAc/ CH_2Cl_2) afforded 737 mg of the desired 1,5-pyrazole (Rf 5% EtOAc/CH_2Cl_2 0.28) and 100 mg of the 1,3-isomer (Rf 5% EtOAc/CH_2Cl_2 0.52).

To a solution of the 1,5-isomer (719 mg, 2.11 mmol) in 10 mL of MeOH cooled in an ice-water bath was added solid K_2CO_3 (283 mg, 2.05 mmol) in one

portion. After stirring for 1 hour, 1.3 mL of a 2N aqueous HOAc solution was added dropwise via syringe. The reaction was then added to 25 mL of water. The resulting mixture was extracted with EtOAc (3 x 25 mL). The EtOAc layers were pooled and washed with brine, dried (Na_2SO_4), filtered and concentrated to dryness. The light yellow oil that formed was triturated with hexane giving 555 mg (88%) of the title compound as a light yellow solid, mp 71-72 °C. ^{1}H NMR ($CDCl_3$): δ 7.55 (d, 1H, J = 1.8 Hz), 7.35 (d, 2H, J = 7.0 Hz), 7.10-7.00 (m, 6H), 6.29 (d, 1H, J = 1.8 Hz), 4.20 (m, 2H), 4.00 (m, 2H), 3.72 (t, 1H, J = 6.2 Hz).

Example 13

3-[4-(4-Fluorophenoxy)phenyl]-1H-pyrazole-1-carboxylic acid dimethylamide

A solution of 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole (467 mg, 1.84 mmol) in 7 mL of THF containing 0.3 mL (2.13 mmol) of triethylamine was treated with 0.3 mL (3.2 mmol) dimethylcarbamyl chloride added via syringe. No reaction was observed at room temperature. An additional 0.3 mL of dimethylcarbamyl chloride was added and the reaction was heated at reflux overnight. The reaction was then added to a saturated aqueous $NaHCO_3$ solution and EtOAc. The aqueous layer was washed with EtOAc and the pooled organic layers were dried (Na_2SO_4), filtered and concentrated to dryness. Column chromatography (7/3 hexane/EtOAc) afforded 282 mg of the title compound as a yellow oil that solidified on standing, mp 59-63 °C. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J = 2.7 Hz), 7.80 (d, 2H, J = 8.4 Hz), 7.06-6.88 (m, 6H), 6.62 (d, 1H, J = 2.7 Hz), 3.30 (br s, 6H).

Example 14

1-Benzyl-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole

To a solution of 3-dimethylamino-1-[4-(4-fluorophenoxy)phenyl]-propenone (580 mg, 2.04 mmol) in EtOH was added benzyl hydrazine dihydrochloride (500 mg, 2.49 mmol). The reaction was heated at reflux until TLC showed complete consumption of the starting enone. The resulting mixture was allowed to cool to room temperature and was added to water/EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined EtOAc layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (gradient from 9:1 to 8:2 hexane/EtOAc) gave 220 mg of the title compound as an oil. ^{1}H NMR ($CDCl_3$): δ 7.59 (d, 1H, J = 1.5 Hz), 7.30-6.90 (m, 13H), 6.32 (d, 1H, J = 1.8 Hz), 5.34 (s, 2H).

Example 15

2-[3-[4-(4-Fluorophenoxy)phenyl]-2H-pyrazol-2-yl]-1-pyrrolidin-1-yl ethanone

A solution of [5-(4-fluorophenoxy)phenyl)pyrazol-1-yl]-acetic acid ethyl ester (104 mg, 0.306 mmol) in 1 mL of MeOH was treated with neat pyrrolidine (0.1 mL, 85 mg, 1.20 mmol). After stirring at room temperature for 4 days, the reaction was concentrated to dryness. The solid residue was triturated with hexane, affording 80 mg (71%) of the amide as a solid, mp 90-95 °C. ^{1}H NMR ($CDCl_3$): δ 7.58 (br s, 1H), 7.46 (d, 2H, J = 8.7 Hz), 7.10-6.98 (m, 6H), 6.30 (br s, 1H), 3.51 (t, 2H, J = 6.6 Hz), 3.44 (t, 2H, J = 6.9 Hz), 1.98 (p, 2H, J = 6.6 Hz), 1.85 (p, 2H, J = 6.6 Hz).

Example 16

2-(N-methylacetamido)-3-[4-(4-fluorophenoxy)phenyl]-2H-pyrazole

The methyl amide was prepared similarly by allowing [5-(4-fluorophenoxy)phenyl)pyrazol-1-yl]-acetic acid ethyl ester to react with methylamine in MeOH, mp 132-135 °C. ^{1}H NMR ($CDCl_3$): δ 7.64 (d, 1H, J = 1.8 Hz), 7.28 (d, 2H,

J = 8.7 Hz), 7.10-7.00 (m, 4H), 7.01 (d, 2H, J = 8.7 Hz), 6.38 (br s, 1H), 6.35 (d, 1H, J = 1.8 Hz), 4.77 (s, 2H), 2.83 (d, 3H, J = 5.4 Hz).

The following amides were prepared using the procedure described for the methyl amide:

2-{5-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1-yl}-1-(4-methyl)piperazine-1-yl-ethanone; R_f 0.30 (10:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 1.8 Hz, 1H), 7.44 (d, J = 9.0 Hz, 2H), 7.10-7.01 (m, 6H), 6.34 (d, J = 1.8 Hz, 1H), 4.96 (s, 2H), 3.68-3.65 (m, 2H), 3.51-3.48 (m, 2H), 2.42 (t, J = 5.0 Hz, 4H), 2.33 (s, 3H).

1-{5-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1-yl}-2-methyl-propane-2-ol; R_f 0.59 (100% EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 1.8 Hz, 1H), 7.35-7.28 (m, 2H), 7.11-7.03 (m, 6H), 6.32 (d, J = 1.8 Hz, 1H), 5.17 (s, 1H), 4.06 (s, 2H), 1.06 (s, 6H).

1-{5-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1-yl}-propane-2-one; R_f 0.53 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 1.8 Hz, 1H), 7.31-7.28 (m, 2H), 7.13-7.01 (m, 6H), 6.37 (d, J = 1.8 Hz, 1H), 4.91 (s, 2H), 2.09 (s, 3H).

1-Morpholin-4-yl-2-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-ethanone; R_f 0.40 (19:1 $CHCl_3$/MeOH); mp 122-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 1.8 Hz, 1H), 7.46 (d, J = 9.0 Hz, 2H), 7.13-7.02 (m, 6H), 6.34 (d, J = 1.5 Hz, 1H), 4.96 (s, 2H), 3.69-3.66 (m, 6H), 3.51-3.50 (m, 2H).

Example 17

2-{5-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1-yl}-acetamide

To a solution of 3-dimethylamino-1-[4-(4-fluorophenoxy)phenyl]-propenone (860 mg, 3.0 mmol) in EtOH was added ethyl hydrazinoacetate hydrochloride (580 mg. 3.64 mmol) as a solid in one portion. After 1 hour at reflux, the reaction was allowed to cool and was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and the combined EtOAc layers were dried (Na_2SO_4),

filtered and concentrated in vacuo. Column chromatography (2% EtOAc/CH_2Cl_2) gave the desired ethyl ester (1,5-isomer; Rf 0.28 5% EtOAc/CH_2Cl_2) and its 1,3-isomer (Rf 0.68 EtOAc/CH_2Cl_2). A solution of the 1,5-isomer in MeOH was treated with an aqueous NH_4OH solution and stirred at room temperature for 48 hours. Work-up after described for the ethyl ester and column chromatography (100% EtOAc) gave 276 mg of the title compound as a white solid, mp 168-169 °C. ^{1}H NMR ($CDCl_3$): δ 7.65 (d, 1H, J = 1.8 Hz), 7.31 (d, 2H, J = 8.7 Hz), 7.10-7.00 (m, 6H), 6.35 (d, 1H, J = 1.8 Hz), 6.30 (br s, 1H), 5.56 (br s, 1H), 4.78 (s, 2H).

Example 18

2-{3-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1-yl}-acetamide

Reaction of the 1,3-isomer using the method described in example 17 for its 1,5-isomer gave 35 mg of the title compound as a white solid, mp 145 °C. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 2H, J = 9 Hz), 7.49 (d, 1H, J = 2.1 Hz), 7.05-6.99 (m, 6H), 6.59 (d, 1H, J = 2.4 Hz), 6.40 (br s, 1H), 5.45 (br s, 1H), 4.83 (s, 3H).

Example 19

3-{5-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1yl}-propionamide

Reaction of 3-dimethylamino-1-[4-(4-fluorophenoxy)phenyl]-propenone with 2-cyanoethylhydrazine as described above gave 1-(2-cyanoethyl)-5-[4-(4-fluorophenoxy)phenyl]pyrazole. Reaction of a solution of the nitrile with 10 mL of a 20% aqueous KOH solution and 4 mL of an aqueous 30% H_2O_2 solution at reflux gave 64 mg of the amide as a white solid, mp 118-120 °C. ^{1}H NMR ($CDCl_3$): δ 7.54 (d, 1H, J = 1.8 Hz), 7.35 (d, 2H, J = 8.7 Hz), 7.10-6.98 (m, 6H), 6.26 (d, 1H, J = 1.8 Hz). 6.08 (br s, 1H), 5.30 (br s, 1H), 4.39 (t, 2H, J = 6.6 Hz), 2.86 (t, 3H, J = 6.6 Hz).

Example 20
2-{3-[4-(4-Fluorophenoxy)phenyl]-pyrazol-1-yl}-pyrimidine

To a solution of 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole (930 mg, 3.66 mmol) in 15 mL of dry THF was slowly added 240 mg (6.00 mmol) of NaH. After stirring at room temperature for 20 minutes, 500 mg (4.15 mmol) of 2-chloropyrimidine was added in one portion. The reaction was allowed to stir overnight at room temperature and concentrated to dryness. The residue was dissolved in $CHCl_3$ and subjected to flash chromatography. Elution with 3:2 hexane/EtOAc gave 994 mg of the title compound as a solid, mp 123-125 °C. ^1H NMR ($CDCl_3$): δ 8.77 (d, 2H, J = 4.8 Hz), 8.65 (d, 1H, J = 3.0 Hz), 7.95 (d, 2H, J = 8.7 Hz), 7.20 (t, 1H, J = 4.9 Hz), 7.07-6.98 (m, 5H), 6.78 (d, 1H, J = 3.0 Hz).

The following compound was prepared using a similar procedure but using 3-[4-(4-trifluoromethylphenoxy)phenyl]-1H-pyrazole:

2-{3-[4-(4-Trifluoromethylphenoxy)phenyl]pyrazol-1-yl}pyrimidine, mp 141-144 °C.

Example 21
4-[4-(4-Fluorophenoxy)phenyl]-1H-imidazole

a) **1-[4-(4-Fluorophenoxy)phenyl]ethanone.** A mixture of 4-fluorophenol (4.45 g, 39.3 mmol), 4-fluoroacetophenone (4.4 mL, 36 mmol), and potassium carbonate (13 g, 94 mmol) in DMF (40 mL) was refluxed overnight. The mixture was allowed to cool to room temperature, then partitioned between ethyl acetate (200 mL) and water (200 mL). The separated aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined ethyl acetate layers were washed with an aqueous sodium hydroxide solution (2N, 200 mL), washed twice with water (200 mL each), dried over sodium sulfate, filtered, and evaporated under reduced pressure to give a dark oil. The oil solidified on standing at room temperature overnight. The weight of crude 1-[4-(4-fluorophenoxy)phenyl]ethanone was 6.7 g (80%). ^1H NMR

($CDCl_3$): δ 7.96 (d, J = 9.0 Hz, 2H), 7.11-7.06 (m, 4H), 6.98 (d, J = 8.7 Hz, 2H), 2.59 (s. 3H).

b) **2-Bromo-1-[4-(4-fluorophenoxy)phenyl]ethanone.** To a solution of 1-[4-(4-fluorophenoxy)phenyl]ethanone (2.1 g, 9.1 mmol) and aqueous hydrobromic acid (3 drops) in methanol (50 mL) was added dropwise a solution of bromine (0.6 mL, 11.6 mmol) in methanol (20 mL). After the addition, the solution was stirred at room temperature overnight. The solution was then partitioned between water and ethyl acetate. The separated aqueous layer was extracted one more time with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate, filtered, and evaporated under reduced pressure to give oil, which solidified on standing (2.5 g, 87%). ^{1}H NMR ($CDCl_3$): δ 7.96 (d, J = 9.0 Hz, 2H), 7.10-7.06 (m, 4H), 6.98 (d, J = 9.0 Hz, 2H), 4.39 (s, 2H).

c) **4-[4-(4-Fluorophenoxy)phenyl]-1H-imidazole.** A solution of 2-bromo-1-[4-(4-fluorophenoxy)phenyl]ethanone (0.547 g, 17.7 mmol) in formamide (25 mL) was refluxed at 190 °C for 1 hour. The solution was allowed to cool to room temperature and partitioned between water and ethyl acetate. The organic layer was washed 3 times with water, dried over sodium sulfate, filtered, and evaporated under reduced pressure to give an oil. The oil was purified by column chromatography (flash silica gel, 9:1 ethyl acetate/methanol) to give 94 mg (21%) of the title compound, mp 165-168 °C. ^{1}H NMR (DMSO-d_6): δ 7.76 (d, J = 8.4 Hz, 2H), 7.71 (s, 1H), 7.52 (s, 1H), 7.23 (t, J = 9.0 Hz, 2H), 7.07 (dd, J = 8.5, 4.9 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H).

The following compounds were prepared similarly:

4-[4-(4-Fluorophenoxy)-3-fluorophenyl]-1H-imidazole; ^{1}H NMR ($CDCl_3$): δ 7.70 (s, 1H), 7.56 (dd, J = 2.0, 12.0 Hz, 1H), 7.46 (dd, J = 1.2, 8.4 Hz, 1H), 7.30 (s, 1H), 7.04-6.93 (m, 5H).

4-[4-(4-Fluorophenoxy)-3-fluorophenyl]-1H-imidazole. hydrochloride salt; the free base prepared above was dissolved in chloroform and a 1N solution of HCl in

ether was added until precipitation occurred. The mixture was evaporated under reduced pressure to afford the salt. ^{1}H NMR (DMSO-d_6): δ 14.8 (bs, 2H), 9.16 (s, 1H), 8.17 (s, 1H), 7.97 (d, J = 11.7 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.25 (t, J = 8.4 Hz, 3H), 7.11 (dd, J = 4.5, 8.7 Hz, 2H).

4-[4-(2,4-Difluorophenoxy)phenyl]-1H-imidazole; ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.66 (s, 1H), 7.26 (s, 1H), 7.09-7.01 (m, 1H), 6.97-6.90 (m, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.98-6.80 (m, 1H); mp 144-148 °C.

4-[4-(2,4-Difluorophenoxy)phenyl]-1H-imidazole, hydrochloride salt; ^{1}H NMR (DMSO-d_6): δ 9.24 (s, 1H), 8.14 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.56-7.48 (m, 1H), 7.42-7.34 (m, 1H), 7.21-7.15 (m, 1H), 7.09 (d, J = 8.7 Hz, 2H); mp 192-195 °C.

4-[4-(4-Chloro-2-fluorophenoxy)phenyl]-1H-imidazole, hydrochloride salt; ^{1}H NMR (DMSO-d_6): δ 9.24 (s, 1H), 8.14 (s, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.67 (dd, J = 10.5, 1.8 Hz, 1H), 7.37-7.26 (m, 2H), 7.14 (d, J = 8.4 Hz, 2H); mp 216-220 °C.

4-(4-(4-Trifluoromethylphenoxy)phenyl]-1H-imidazole, hydrochloride salt; ^{1}H NMR (DMSO-d_6): δ 15.0 (bs, 2H), 9.25 (s, 1H), 8.18 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H); mp 230-232 °C. The intermediate 1-[4-(4-trifluoromethylphenoxy)phenyl]ethanone was prepared from 4-hydroxyacetophenone and 4-fluorobenzotrifluoride using the method described for the synthesis of 1-[4-(4-fluorophenoxy)phenyl]ethanone.

Example 22

4-[4-(2,4-Difluorophenoxy)phenyl]-2-methyl-1H-imidazole

A solution of acetamidine hydrochloride (120 mg, 1.71 mmol) in DMF was treated with 2 mL (2.0 mmol) of a 1M solution of potassium *tert*-butoxide in THF. The resulting mixture was heated at 95 °C for 1hour. Solid 2-bromo-1-[4-(4-fluorophenoxy)-3-fluorophenyl]ethanone (prepared as described for 2-bromo-1-[4-(4-fluorophenoxy)phenyl]ethanone; 345 mg, 1.00 mmol) was added and the reaction was stirred at 95 °C overnight. Once at room temperature, the mixture was partitioned between water and EtOAc. The separated aqueous layer was extracted once with

EtOAc and the pooled organic layers were washed with water (3 x), dried (Na_2SO_4), filtered and concentrated. Column chromatography (100% EtOAc) gave 86 mg of the imidazole as a solid, TLC R_f 0.54 (5% MeOH/EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.53 (dd, 1H, J = 11.9, 1.6 Hz), 7.43 (d, 1H, J = 8.4 Hz), 7.16 (s, 1H), 7.03-6.92 (m, 5H), 2.47 (s, 3H).

Example 23

4-[4-(2,4-Difluorophenoxy)phenyl]-1-methyl-1H-imidazole-2-carboxamide

a) 2-Cyano-4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole. A mixture of crude 4-[4-(2,4-difluorophenoxy)phenyl]-1H-imidazole (prepared from 4.14 g of 2-bromo-1-[4-(2,4-difluorophenoxy)phenyl]ethanone and 35 mL of formamide as described above), solid KOH (2.57 g) and MeI (1 mL) was heated at reflux overnight. After filtration, the reaction was concentrated to dryness and the residue was purified by flash chromatography, affording 4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole as a solid. A solution of 4-(dimethylamino)pyridine (1.34 g, 10.9 mmol) in 30 mL of dry DMF at −10 °C was added cyanogen bromide (5.0 M solution in MeCN; 2.1 mL, 10.5 mmol), giving a pale yellow precipitate. Solid 4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole (1.39 g, 4.86 mmol) was added and the reaction was heated at 60 °C overnight. The reaction was allowed to cool to room temperature and added to water and EtOAc. The separated aqueous layer was extracted twice with EtOAc and the pooled organic layers were washed with water (3 x), dried (Na_2SO_4), filtered and concentrated. The oily residue was purified by flash chromatography (gradient from 8.5/2.5 to 7/3 hexane/EtOAc) affording 713 mg of 2-cyano-4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole as a solid, mp 109-110 °C (Rf 0.42, 7/3 hexane/EtOAc) along with 122 mg of 4-cyano-4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole, mp 169-170 °C (Rf 0.32, 7/3 hexane/EtOAc). ^{1}H NMR (2-cyano; $CDCl_3$): δ 7.65 (d, 2H, J = 9.0 Hz), 7.16 (s, 1H), 7.06 (dt, 1H, J = 9.3, 5.4 Hz), 6.93 (d, 2H, J = 8.7 Hz), 6.98-6.80 (m, 2H), 3.65 (s,

3H). ^{1}H NMR (4-cyano; $CDCl_3$): δ 7.69 (d, 2H, J = 8.7 Hz), 7.27 (s, 1H), 7.09 (dt, J = 8.7, 5.7 Hz), 6.96 (d, 2H, J = 8.7 Hz), 7.00-6.82 (m, 2H), 3.90 (s, 3H).

b) 4-[4-(2,4-Difluorophenoxy)phenyl]-1-methyl-1H-imidazole-2-carboxamide. A mixture of 2-cyano-4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole (0.40 g, 1.27 mmol), ethylenediamine (0.3 mL, 4.5 mmol), *p*-toluenesulfonic acid monohydrate (110 mg, 0.58 mmol) in ethylene glycol was heated at reflux for 20 hours. Work-up as described above and column chromatography (gradient from 100% EtOAc to 5% MeOH/EtOAc) gave 47 mg of the title compound as a yellow solid, mp 183-187 °C. ^{1}H NMR ($CDCl_3$): δ 10.44 (br s, 1H), 7.38 (d, 2H, J = 9.0 Hz), 7.10-6.80 (m, 5H), 6.40 (s, 1H), 3.32 (s, 3H).

Example 24

2-[4-(4-Fluorophenoxy)phenyl]-1H-imidazole

A mixture of 4-(4-fluorophenoxy)benzonitrile (720 mg, 3.38 mmol), ethylenediamine (0.3 mL, 4.4 mmol) and *p*-toluenesulfonic acid monohydrate (420 mg, 2.20 mmol) in ethylene glycol was heated at reflux for 48 hours. Once at room temperature, the reaction was added an aqueous 2N NaOH solution. The resulting precipitate was isolated by filtration and was carried on without further purification. A solution of the imidazoline (0.53 g, 2.0 mmol) in 20 mL of toluene was treated with 10% Pd/C (0.53 g) and heated at reflux for 40 hours. The reaction was partitioned between 100 mL of EtOAc and 200 mL of an aqueous 2N NaOH solution. The separated organic layer was filtered through a bed of Celite and evaporated to give a solid. A solution of the free base in MeOH was treated with HCl/ether and evaporated to give the hydrochloride salt, mp 86-91 °C. ^{1}H NMR (DMSO-d_6): δ 14.8 (br s, 2H), 8.11 (d, 2H, J = 8.7 Hz), 7.76 (s, 2H), 7.31 (t, 2H, J = 8.9 Hz), 7.22-7.19 (m, 2H), 7.19 (d, 2H, J = 9.0 Hz).

Example 25

2-[4-(4-Fluorophenoxy)phenyl]-1H-benzimidazole

A mixture of 4-(4-fluorophenyl)benzoic acid (190 mg, 0.88 mmol) and phenylenediamine (133 mg, 1.22 mmol) in 25 g of polyphosphoric acid was heated at 150 °C overnight. Once at room temperature, the reaction was diluted with water. The resulting solid was washed with water, dried and chromatographed (gradient from 8/2 to 7/3 hexane/EtOAc) affording 104 mg (39%) of the benzimidazole as a solid, mp 243-245 °C. R_f 0.40 7/3 hexane/EtOAc. ^{1}H NMR (DMSO-d_6): δ 12.8 (s, 1H), 8.16 (d, J=8.4 Hz, 2H), 7.61 (m, 1H), 7.49 (m, 1H), 7.29 (t, J=8.4 Hz, 2H), 7.20-7.16 (m, 4H), 7.12 (d, J=8.4 Hz, 2H).

Example 26

2-[4-(4-Fluorophenoxy)phenyl]-1H-imidazole-4-carboxamide

To a solution of 0.56 g (6.83 mmol) of sodium acetate in 10 mL of water was added 1.29 g (4.78 mmol) of 1,1-dibromo-3,3,3-trifluoroacetone. The resulting solution was warmed for 30 minutes and then cooled in an ice/water bath. A solution of 4-(fluorophenoxy)benzaldehyde (789 mg, 3.65 mmol) in MeOH was added, followed by 10 mL of a concentrated aqueous NH_4OH solution. Additional MeOH was added until a homogenous solution formed. After stirring at room temperature overnight, the reaction was diluted with water. The precipitate that formed was collected, washed with water and dried. Column chromatography (gradient from 8/2 to 2/3 hexane/EtOAc) afforded 0.6 g of a solid. A mixture of 0.5 g of the solid and 80 mL of a concentrated aqueous NH_4OH solution was diluted with MeOH until a solution formed. The reaction was heated in a sealed tube for 1.5 days. After cooling to room temperature, the mixture was added to a water/EtOAc mixture. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated to dryness. Column chromatography (1:1 hexane/EtOAc) gave 2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole-4-carbonitrile

as a solid. ^{1}H NMR (DMSO-d_6): δ 13.37 (br s, 1H), 8.23 (s, 1H), 7.95 (d, 2H, J = 8.7 Hz), 7.27 (t, 2H, J = 8.9 Hz), 7.15 (dd, 2H, J = 9.3, 4.5 Hz), 7.08 (d, 2H. J = 8.7 Hz). To a solution of the nitrile in EtOH was added 1 g of KOH dissolved in 5 mL of water and 1.5 mL of a 30% aq. H_2O_2 solution. After heating at reflux for 3 hours, the reaction was added to water/EtOAc. The organic layer was dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was subjected to flash chromatography (100% EtOAc) affording the title compound as a white solid. TLC R_f 0.34 (5% MeOH/EtOAc). ^{1}H NMR ($CDCl_3$): δ 12.90 (br s, 1H), 8.08 (br s, 1H), 7.97 (d, 2H, J = 9.0 Hz), 7.70 (s, 1H), 7.63 (br s, 1H), 7.26 (t, 2H, J = 8.7 Hz), 7.15-7.10 (m, 2H), 7.07 (d, 2H, J = 8.7 Hz).

Example 27

5-[4-(4-fluorophenoxy)phenyl]-pyrrole-2-carboxamide

a) **5-(Butoxycarbonyl)-1-(*tert*-butoxycarbonyl)-2-pyrrolidone.** To a solution of butyl 2-pyrrolidone-5-carboxylate (Aldrich; 7.41 g, 40 mmol) in dry CH_2Cl_2 (150 mL) was added di-*tert*-butyl dicarbonate (13.5 g, 61.5 mmol) and Et_3N (12 mL). After stirring at room temperature for 3 days, the reaction was concentrated to dryness. The resulting residue was chromatographied (hexane-EtOAc, 1:1) affording 9.8 g (86%) of 5-(butoxycarbonyl)-1-(*tert*-butoxycarbonyl)-2-pyrrolidone as a yellowish oil. ^{1}H NMR($CDCl_3$): δ 4.63 (dd, 1H, J = 9 Hz, 3 Hz), 4.19 (t, 2H, J = 7 Hz), 2.72-2.27 (m, 2H), 2.10-2.00 (m, 2H), 1.69-1.62 (m, 2H), 1.52 (s, 9H), 1.48-1.37 (m, 2H), 0.96 (t, 3H, J = 7.5 Hz).

b) **4-Fluorodiphenyl ether.** A mixture of 4-fluorophenol (5.6 g, 50 mmol), potassium *tert*-butoxide (5.6 g, 50 mmol), bromobenzene (7.85 g, 50 mmol) and copper powder (2 g) in DMSO (20 mL) was refluxed for 18 hours, allowed to cool to room temperature, diluted with EtOAc (150 mL), and filtered. The filtrate was evaporated and the residue was chromatographed (hexane) to give 6.0 g (63.8%) of the ether as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.25 (dt, 2H, J = 8 Hz, 2.5 Hz), 7.11 (dt, 1H, J = 8 Hz, 2.5 Hz), 7.06-6.98 (m, 6H).

c) **4-Bromo-4′-fluorodiphenyl ether.** To a solution of 4-fluorodiphenyl ether (6.0 g, 32 mmol) and a crystal of I_2 in CS_2 (20 mL) cooled in an ice-water bath was slowly added bromine (2 mL). After stirring at room temperature for 16 hours the reaction was concentrated in vacuo and the residue was chromatographied (hexane) to give 7 g (80%) of the ether as a colorless oil. ^{1}H NMR($CDCl_3$): δ 7.46-7.42 (m, 2H), 7.10-6.97 (m, 4H), 6.88-6.84 (m, 2H).

d) **Butyl 5-[4-(4-fluorophenoxy)phenyl]-5-keto-2-Boc-amino-pentanoate.** To a solution of 4-bromo-4'-fluorodiphenyl ether (3.88 g, 14.5 mmol) in dry THF (60 mL) was added Mg metal (500 mg, 20.6 mmol) and a small piece of I_2. The mixture was refluxed for 16 hours and allowed to cooled. The liquid phase was transferred with a syringe into a solution of 5-(butoxycarbonyl)-1-(*tert*-butoxycarbonyl)-2-pyrrolidone (3.9 g, 13.7 mmol) in dry THF (80 mL) cooled below 0 °C. The reaction mixture was stirred at room temperature for 5 hours then at reflux. Once at room temperature, the reaction mixture was treated with 10 mL of 50% AcOH and MeOH (10 mL), stirred for 30 minutes and evaporated. The residue was dissolved in EtOAc (300 mL), washed with brine (2x50 mL), evaporated, and chromatographed (hexane-EtOAc, 7:3) affording 2.4 g (39%) of the desired ester as a colorless oil. ^{1}H NMR($CDCl_3$): δ 7.95 (d, 2H, J = 8 Hz), 7.11-6.85 (m, 6H), 4.95-4.90 (m, 1H), 4.20 (t, 2H, J = 7 Hz), 3.21-2.94 (m, 2H), 2.35-2.00 (m, 2H), 1.73-1.64 (m, 3H), 1.51 (s, 9H), 1.48-1.36 (m, 2H), 0.95 (t, 3H, J = 7.5 Hz).

e) **Butyl 5-[4-(4-fluorophenoxy)phenyl]-ρ^1-pyrroline-2-carboxylate.** To a cooled (ice-water bath) solution of butyl 5-[4-(4-fluorophenoxy)phenyl]-5-keto-2-Boc-aminopentanoate (2.4 g, 5.36 mmol) in dry CH_2Cl_2 (12 mL) was added trifluoroacetic acid (5 mL). After stirring cold for 2 hours, the reaction was diluted with CH_2Cl_2 (200 mL). The CH_2Cl_2 solution was washed with a saturated aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4), filtered and evaporated to give 1.69 g (84 %) of the desired pyrroline as a yellowish oil. ^{1}H NMR($CDCl_3$): δ 7.87 (d, 2H, J = 9 Hz), 7.12-6.80 (m, 5H), 4.95-4.90 (m, 1H), 4.20 (t, 2H, J = 7 Hz), 3.21-2.94 (m, 2H), 2.35-2.00 (m, 2H), 1.73-1.64 (m, 3H), 1.48-1.36 (m, 2H), 0.96 (t, 3H, J = 7.5 Hz).

f) Butyl 5-[4-(4-fluorophenoxy)phenyl]-pyrrole-2-carboxylate. A solution of pyrroline ester (1.69 g, 4.76 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1.71 g, 5.16 mmol) in dry CH_2Cl_2 (100 mL) was stirred at room temperature for 1 hour. A solid that formed was removed by filtration, and the filtrate was evaporated to dryness. The residue was chromatographed (hexane-EtOAc, 4:1) to give 400 mg (24%) of the pyrrole ester as a solid, mp.133-134°C. ^{1}H NMR($CDCl_3$): δ 9.34 (bs, 1H), 7.55 (dd, 2H, J = 9 Hz, 2 Hz), 7.11-6.96 (m, 6H), 6.50-6.49 (m, 1H), 4.31 (t, 2H, J = 7 Hz), 1.80-1.71 (m, 2H), 1.55-1.42 (m, 2H), 1.00 (t, 3H, J = 7.5 Hz).

g) 5-[4-(4-Fluorophenoxy)phenyl]-pyrrole-2-carboxylic acid. To a solution of the pyrrole ester (900 mg, 2.55 mmol) in MeOH (60 mL) was added a 2N aqueous NaOH solution (15 mL) and the resulting mixture was refluxed for 1.5 hours. Once at room temperature, the reaction was acidified to pH 4 with an aqueous 1N HCl solution. The resulting precipitate was collected by filtration, washed with H_2O and dried to give 700 mg (92%) of the acid as a grey solid, mp.154-155°C. ^{1}H NMR (DMSO-d_6): δ 7.86 (d, 2H, J = 9 Hz), 7.29-7.23 (m, 2H), 7.14-7.09 (m, 2H), 7.00 (d, 2H, J = 9 Hz), 6.84 (d, 1H, J = 3.6 Hz), 6.58 (d, 1H, J = 3.6 Hz).

h) 5-[4-(4-Fluorophenoxy)phenyl]-pyrrole-2-carboxamide. To a solution of the acid (356 mg, 1.2 mmol) in DMF (10 mL) was added 1,1'-carbonyldiimidazole (CDI, 406 mg, 2.5 mmoL). The solution was heated at reflux for 1 hour, followed by the addition of solid NH_4OAc (1.2 g, 15.6 mmoL). After an additional 16 hours at reflux, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL), washed with brine, evaporated, and the residue was chromatographed (1/1 hexane/EtOAc) to give 180 mg (51%) of the amide as an off-white powder, mp 218-220 °C. ^{1}H NMR (DMSO-d_6): δ 11.59 (s, 1H), 7.82 (d, 2H, J = 9 Hz), 7.52 (bs, 2H), 7.25 (t, 2H, J = 9 Hz), 7.10-7.04 (m, 2H), 6.97 (d, 2H, J = 9 Hz), 6.83 (dd, 1H, J = 4 Hz, 1 Hz), 6.50 (dd, 1H, J = 4 Hz, 1.2 Hz).

Example 28

Methyl 5-[4-(4-fluorophenoxy)phenyl]pyrrole-2-carboxylate

A mixture of 5-[4-(4-fluorophenoxy)phenyl]-pyrrole-2-carboxylic acid (300 mg, 1.0 mmol) and $SOCl_2$ (2 mL) was stirred at room temperature for 1 h and the resulting solution was evaporated to dryness. The residue was cooled in an ice-water bath, and a 2M solution of NH_3 in MeOH (5 mL) was added slowly. The reaction was stirred for 2 hours and then evaporated to dryness. The residue was taken up into $CHCl_3$, the $CHCl_3$ solution was evaporated, and the residue was chromatographed (7/3 hexane/EtOAc) to give 200 mg (64%) of the methyl ester as a light yellow solid, mp144-145 °C. ^1H NMR ($CDCl_3$): δ 9.23 (bs, 1H), 7.54 (d, 2H, J = 9 Hz), 7.11-6.96 (m, 5H), 6.51-6.49 (m, 1H), 3.90 (s, 3H).

Example 29

2-[4-(4-Fluorophenoxy)phenyl]oxazole-4-carboxamide

a) **4-(4-Fluorophenoxy)benzoic acid.** A solution of 4-(4-fluorophenoxy)benzaldehyde (1.1 g, 5.1 mmol) in pyridine (25 mL) was treated with solid potassium permanganate (1.0 g, 6.3 mmol). The resulting mixture was stirred at room temperature for 16 hours. The mixture was then partitioned between an aqueous 2N HCl solution and a hexane/ethyl acetate solution. The aqueous layer was extracted two more times with hexane/ethyl acetate. The combined organic layers were filtered through a bed of Celite. The filtrate was washed with an aqueous 2N HCl solution, dried over sodium sulfate, filtered, and evaporated under reduced pressure to give 790 mg (67%) of the desired product as a white solid. ^1H NMR (DMSO-d_6): 12.80 (bs, 1H). 7.94 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 8.7 Hz, 2H), 7.21-7.17 (m, 2H), 7.01 (d, J = 8.4 Hz, 2H).

b) ***N*-[4-(4-Fluorophenoxy)benzoyl]-L-serine methyl ester.** To an ice cold solution of 4-(4-fluorophenoy)benzoic acid (0.79 g, 3.4 mmol), L-serine methyl ester hydrochloride (0.59 g, 3.7 mmol), and a 1-hydroxybenzotriazole hydrate (0.57 g,

3.7 mmol) in DMF (20 mL) was added *N*-methylmorpholine (82 mL, 7.4 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.72 g, 3.7 mmol). The resulting solution was allowed to warm to room temperature overnight and was then partitioned between water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate and the combined ethyl acetate layers were washed with water (3 x), dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the desired product as an oil. ^{1}H NMR (DMSO-d_6): 8.51 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.28 (t, J = 8.4 Hz, 2H), 7.18-7.13 (m, 2H), 7.04 (d, J = 9.0 Hz, 2H), 5.06 (t, J = 6.3 Hz, 1H), 4.53 (q, J = 7.8 Hz, 1H), 3.79 (t, J = 5.4 Hz, 2H), 3.71 (s, 3H).

c) Methyl 4,5-dihydro-2-[4-(4-fluorophenoxy)phenyl]oxazole-4-carboxylate. To a solution of *N*-[4-(4-fluorophenoxy)benzoyl]-L-serine methyl ester (assumed to be 37 mmol from the previous reaction) and triphenylphosphine (0.38 g, 6.8 mmol) in acetonitrile (40 mL) was added diisopropylethyl amine (1.2 ml, 6.8 mmol) and carbon tetrachloride (0.66 mL, 6.8 mmol). The resulting solution was stirred at room temperature for 48 hours when TLC analysis indicated incomplete reaction. Triphenylphosphine (1.9 g, 7.2 mmol), diisopropylethyl amine (1.2 mL, 6.8 mmol) and carbon tetrachloride (0.66 mL, 6.8 mmol) was added to the reaction. The solution was stirred at room temperature for 16 hours and concentrated to dryness. The resulting solid was purified by column chromatography affording 910 mg (89%) of the desired product. ^{1}H NMR (DMSO-d_6): 7.88 (d, J = 8.7 Hz, 2H), 7.29 (t, J=9.3 Hz, 2H), 7.20-7.17 (m, 2H), 7.03 (d, J=8.7 Hz, 2H), 4.95 (dd, J = 8.1 Hz, 1H), 4.64-4.25 (m, 2H), 3.71 (s, 3H).

d) Methyl 2-[4-(4-fluorophenoxy)phenyl]oxazole-4-carboxylate. A mixture of methyl 4,5-dihydro-2-[4-(4-fluorophenoxy)phenyl]oxazole-4-carboxylate (0.91 g, 2.88 mmol), manganese dioxide (2.2 g, 85%, 21.5 mmol) and 4Å molecular sieves (1.2 g) in benzene (30 mL) was refluxed for 3 hours. An additional 1.2 g (11.7 mmol) of manganese dioxide was added and the reaction was heated at reflux for an additional 2 hours. After the mixture was cooled to room temperature, water was

added to the mixture. The mixture was filtered through a bed of Celite. The filtrate was extracted twice with dichloromethane and the combined dichloromethane layers were dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the product as a light yellow solid. ^{1}H NMR ($CDCl_3$): 8.28 (s, 1H), 8.09 (d, J = 8.7 Hz, 2H), 7.11-7.02 (m, 6H), 3.98 (s, 3H).

e) **2-[4-(4-Fluorophenoxy)phenyl]-oxazole-4-carboxamide.** The crude methyl ester prepared above was dissolved in MeOH and an aqueous ammonium hydroxide solution (10 mL) was added. After stirring at room temperature for several hours, TLC analysis showed incomplete reaction. An additional 10 mL of an aqueous ammonium hydroxide solution was added, and the solution was stirred at room temperature for 16 hours. The solution was then partitioned between water and ethyl acetate. The aqueous layer was extracted 2 times with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the crude product. Purification by column chromatography gave 227 mg (26%) of the title compound as a white solid, mp 164°C. ^{1}H NMR ($CDCl_3$): 8.27 (s, 1H), 8.02 (d, J = 9.0 Hz, 2H), 7.15-7.04 (m, 6H), 6.93 (bs, 1H), 5.61 (bs, 1H).

Example 30

4-[4-(4-Fluorophenoxy)-3-fluorophenyl]-thiazole-2-carboxamide

a) **2-Bromo-1-[4-(4-fluorophenoxy)-3-fluorophenyl]-ethanone.** A solution of 1-[4-(4-fluorophenoxy)-3-fluorophenyl]-ethanone (2.68 g, 10.8 mmol, prepared as described for 1-[4-(4-fluorophenoxy)phenyl]-ethanone) in methanol containing an aqueous 48% HBr solution (4 drops) was treated with a solution of bromine (0.61 mL, 11.8 mmol) in methanol. After stirring at room temperature for several hours, the solution was evaporated *in vacuo*. The residue was partitioned between water and ethyl acetate. The ethyl acetate layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to give 3.45 g (97%) of the

crude bromide. ^{1}H NMR ($CDCl_3$): 7.82 (dd, J = 11.4, 2.4 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.28-7.07 (m, 3H), 6.92 (t, J = 8.4 Hz, 2H), 4.37 (s, 2H).

b) Ethyl 4-[4-(4-fluorophenoxy)-3-fluorophenyl]-thiazole-2-carboxylate. A solution containing 2-bromo-1-[4-(4-fluorophenoxy)-3-fluorophenyl]ethanone (1.30 g, 3.97 mmol) and ethyl thioxamate (0.60 g, 4.3 mmol) in ethanol was refluxed for 16 hours. The solution was then partitioned between water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate/hexane. The combined organic layers were dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the crude product. This material was carried on to the next step without purification. ^{1}H NMR ($CDCl_3$): 7.80 (d, J = 11.7 Hz, 1H), 7.69 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.06-6.97 (m, 5H), 4.51 (q, J = 6.9 Hz, 2H), 1.47 (t, J = 6.9 Hz, 3H).

c) 4-[4-(4-Fluorophenoxy)-3-fluorophenyl]-thiazole-2-carboxamide. A solution of crude ethyl 4-[4-(4-fluorophenoxy)-3-fluorophenyl]-thiazole-2-carboxylate in methanol (40 mL) and an aqueous ammonium hydroxide solution (10 mL) was stirred at room temperature for several hours. The solution was evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted once with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate, filtered, evaporated under reduced pressure, and purified by column chromatography to give 765 mg (58%) of the title compound as a yellow solid, mp 183°C. ^{1}H NMR ($CDCl_3$): 7.76 (dd, J = 11.7, 2.1 Hz, 1H), 7.70 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.18 (bs, 1H), 7.08-7.00 (m, 5H), 5.66 (bs, 1H).

Example 31

3-[4-(2,4-Difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide as anticonvulsant

The ability of 3-[4-(2,4-difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide to block maximal electroshock-induced seizures (MES) was determined as described earlier.

3-[4-(2,4-Difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide was administered p.o. to mice 30 minutes before the test procedure. The compound exhibited protection against MES with an ED_{50} (the dose provided protection of 50% of animals) of 3.5 mg/kg.

The following compounds in Table 1 were tested in MES as described for 3-[4-(2,4-difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide:

Table 1.

Anticonvulsant Evaluation after Oral Administration to Mice

Compound name	MES p.o. ED_{50} / mg/kg
4-[4-(4-fluorophenoxy)phenyl]-1H-imidazole	4.2
4-[4-(4-fluorophenoxy)-3-fluorophenyl]-1H-imidazole	3.2
4-[4-(2-fluoro-4-chlorophenoxy)phenyl]-1H-imidazole, hydrochloride	10
4-(4-(4-trifluoromethylphenoxy)phenyl]-1H-imidazole, hydrochloride	7.7
4-[4-(2,4-difluorophenoxy)phenyl]-2-methyl-1H-imidazole	7.5
Methyl 5-[4-(4-fluorohenoxy)phenyl]pyrrole-2-carboxylate	6.0
5-[4-(4-fluorohenoxy)phenyl]-pyrrole-2-carboxamide	10
3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide	7.0
3-[4-(4-chloro-2-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide	3.1
3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole-1-carboxamide	2.0
5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole	8.0
3-[3-fluoro-4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide	4.5
2-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-acetamide	2.6
2-{3-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-pyrimidine	4.7
3-[4-(4-trifluoromethylphenoxy)phenyl]-1H-pyrazole-1-carboxamide	3.9
2-(N-methylacetamido)-3-[4-(4-fluorophenoxy)phenyl]-2H-pyrazole	2.9
3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxylic acid dimethylamide	8.6
1-[2-(methanesulfonylamino)ethyl]-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole	7.5
1-morpholin-4-yl-2-{5-[4-(4-fluoro-phenoxy)phenyl]pyrazol-1-yl}-ethanone	4.4
2-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-1-(4-methyl)-piperazin-1-yl-ethanone	10

Example 32

Activity of 3-[4-(4-Fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide as Sodium Channel Blocker

3-[4-(4-Fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide was tested in the electrophysiological and binding assays described above and produced dose-dependent inhibition of voltage-gated sodium currents recorded in HEK-293 cells stably expressing hSkM1 sodium channels. The blocking effect of this compound on Na^- currents was highly sensitive to the holding voltage, indicating that 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide binds to voltage-sensitive Na^+ channels in their inactivated states and has weak potency towards Na^+ channels in their resting states (Ragsdale *et al.*, *Mol. Pharmacol. 40*:756-765 (1991); Kuo and Bean, *Mol. Pharmacol. 46*:716-725 (1994)). The apparent antagonist dissociation constant (K_d) of this compound for inactivated sodium channels is ~ 8 nM.

The K_i (the concentration of a compound that produces half maximal inhibition) value for 3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide and other tested compounds are presented in Table 2.

Table 2.

Evaluation of the Tested Compounds as Sodium Channel Blockers after an Electrophysiological in vitro Assay

Compound name	HSkM1 K_i / μM
3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide	0.008
3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide	0.015
3-[4-(2,4-difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide	0.010
3-[4-(4-chloro-2-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide	0.003
5-methylthio-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide	0.08
3-[4-(nitrophenoxy)phenyl]-1H-pyrazole-1-carboxamide	0.011
1-{3-[4-(4-nitrophenoxy)phenyl]-pyrazol-1-yl}ethanone	0.009
5-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole	0.11
4-[4-(4-fluorophenoxy)-3-fluorophenyl]thiazole-2-carboxamide	0.02

Example 33

Activity of 4-[4-(4-Fluorophenoxy)-3-fluorophenyl]-1H-imidazole, hydrochloride salt as Sodium Channel Blocker

4-[4-(4-Fluorophenoxy)-3-fluorophenyl]-1H-imidazole, hydrochloride salt was tested in the electrophysiological and binding assays described above and produced dose-dependent inhibition of voltage-gated sodium currents recorded in HEK-293

cells stably expressing the rBIIA isoform of Na^+ channels. The blocking effect of this compound on Na^+ currents was highly sensitive to the holding voltage, indicating that 4-[4-(4-fluorophenoxy)-3-fluorophenyl]-1H-imidazole hydrochloride binds to voltage-sensitive Na^+ channels in their inactivated states and has weak potency towards Na^+ channels in their resting states (Ragsdale *et al.*, *Mol. Pharmacol.* *40*:756-765 (1991); Kuo and Bean, *Mol. Pharmacol.* *46*:716-725 (1994)). The apparent antagonist dissociation constant (K_d) of this compound for inactivated sodium channels is 250 nM.

The K_i (the concentration of a compound that produces half maximal inhibition) value for 4-[4-(4-fluorophenoxy)-3-fluorophenyl]-1H-imidazole hydrochloride and other tested compounds are presented in Table 3.

Table 3.

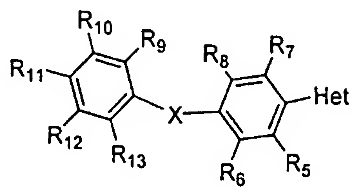
Evaluation of the Tested Compounds as Sodium Channel Blockers after an Electrophysiological in vitro Assay

Compound name	RBIIA K_i / μM
4-[4-(4-fluorophenoxy)-3-fluorophenyl]-1H-imidazole, hydrochloride	0.25
2-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}acetamide	1.56
2-{3-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}pyrimidine	0.42
4-[4-(2,4-difluorophenoxy)phenyl]-1H-imidazole	1.03
4-[4-(2-fluoro-4-chlorophenoxy)phenyl]-1H-imidazole, hydrochloride	0.12
2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole, hydrochloride	1.1
2-[4-(4-fluorophenoxy)phenyl]oxazole-4-carboxamide	1.31

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

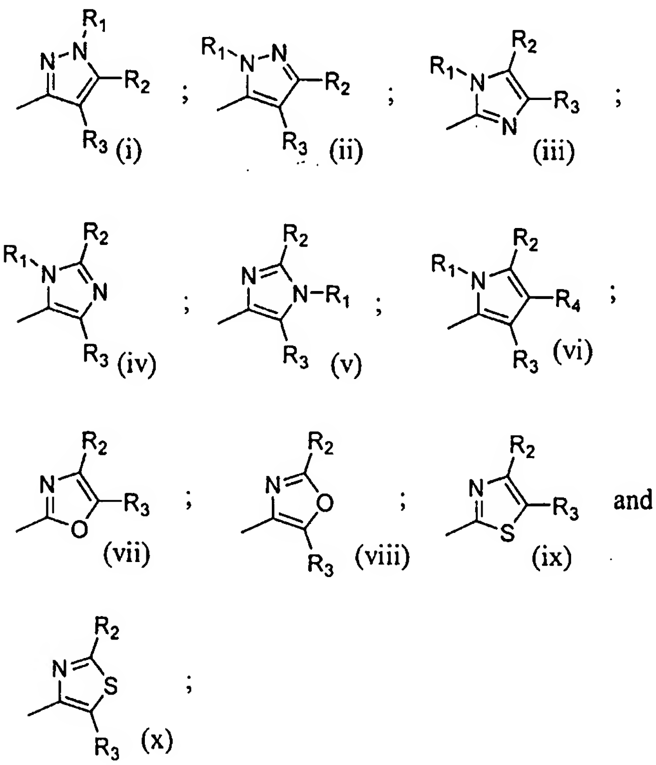
1. A compound having the Formula ***I***:



I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Het is a heteroaryl selected from the group consisting of



R_1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14} all of which may be optionally substituted;

R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, cyano, amino, alkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, or the R groups in adjacent carbon atoms can be taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; or R_9 and R_{10} or R_{10} and R_{11} are taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkynyl, arylalkylamino, dialkylaminoalkenyl, heterocycle, heterocycloalkylamino, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$, wherein R_{15} is hydrogen, alkyl or cycloalkyl,

with the provisos that:

1) when Het is (i) or (ii),

a) R_1 is H and X is O or S, at least one of R_2, R_3 and R_5-R_{13} is other than H, except that R_{11} is not NO_2 when R_3 is CH_3, and R_3 is not $-CH_2CH_2COOH$ when the other substituents are each H;

b) R_1 is H, X is O and one of R_9-R_{13} is NO_2 or OCH_3, at least one the other substituents is other than H;

c) X is O, R_9 or R_{13} is CN and a Cl group is *ortho* to CN, at least one of R_2, R_3 and R_5-R_8 is other than H;

d) X is O, R_5 and R_{11} are Cl, at least one of R_6, R_7, R_8, R_9, R_{10}, R_{12} and R_{13} is other than H;

e) X is O, R_2 is methylthio, R_1 is H or $C(O)R_{14}$ wherein R_{14} is optionally substituted phenyl, at least one of R_5-R_{13} is other than H; or

f) R_1 is $C(O)NH_2$ and X is O, at least one of R_2, R_3 and R_5-R_{13} is other than H;

2) when Het is (iii),

a) R_1 is H, X is O or CH_2 and R_2 and R_3 together form $-CH=CH-CH=CH-$, R_5-R_{13} are not all H;

b) R_1 is Et and R_2 and R_3 together form $-CH=CH-CH=CH-$, X is not -NEt; or

c) R_1 is H and X is O, R_2-R_{13} are not all H;

3) when Het is (iv) and R_1 is H or alkyl, R_2-R_{13} are not all H; or

4) when Het is (vi),

a) X is O, S, or CH_2, R_2 and R_4 do not together form $-CH=CH-CH=CH-$;

b) R_1 is H and X is O or S, R_2-R_{13} are not all H; or

c) X is S and R_1 and R_2 both are Me, at least one of R_3 and R_4 is other than $-CH_2OH$.

2. The compound of claim 1, wherein the two R groups attached to adjacent carbon atoms taken together form $-OCH_2O-$, $-OCF_2O-$,

$-(CH_2)_3-$, $-(CH_2)_4-$, $-OCH_2CH_2O-$, $-CH_2N(R_{15})CH_2-$, $-CH_2CH_2N(R_{15})CH_2-$, $-CH_2N(R_{15})CH_2CH_2-$ and $-CH=CH-CH=CH-$, wherein R_{15} is hydrogen, alkyl or cycloalkyl.

3. The compound of claim 1, wherein R_9 and R_{10} or R_{10} and R_{11} taken together are $-OCH_2O-$, $-OCF_2O-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-OCH_2CH_2O-$, $-CH_2N(R_{15})CH_2-$, $-CH_2CH_2N(R_{15})CH_2-$, $-CH_2N(R_{15})CH_2CH_2-$ and $-CH=CH-CH=CH-$, wherein R_{15} is hydrogen, alkyl or cycloalkyl.

4. The compound of claim 1, wherein Het is selected from the group consisting of (i), (ii), (iv) and (v).

5. The compound of claim 1, wherein R_1 is selected from the group consisting of an alkyl optionally substituted by halogen, hydroxy, carbamoyloxy, C_{1-6} acyl, C_{1-6} alkylsulfonylamino, aryl, or aminocarbonyl, heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, or SO_2R_{14}, wherein R_{14} is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, OR_{16}, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkenylamino, di(C_{1-6})alkylaminoalkenyl, heterocycle, or heterocyclo(C_{1-6})alkylamino, all of which can be optionally substituted, and wherein R_{14} and R_{16} are as defined in claim 1.

6. The compound of claim 1, wherein R_{14} is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, OR_{16}, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkenylamino, di(C_{1-6})alkylamino(C_{2-6})alkenyl, heterocycle, and heterocyclo(C_{1-6})alkylamino, all of which can be optionally substituted, wherein R_{16} is as defined in claim 1.

7. The compound of claim 5, wherein R_1 is $C(O)R_{14}$ or SO_2R_{14}, wherein R_{14} is as defined in claim 1 and X is O or S.

8. The compound of claim 7, wherein R_{14} is amino or C_{1-6} alkyl.

9. The compound of claim 5, wherein R_1 is optionally substituted heteroaryl, optionally substituted C_{1-6} alkyl, or $CH_2C(O)R_{14}$, wherein R_{14} is an optionally substituted heterocycle, optionally substituted C_{1-6} alkyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, or OR_{16}, wherein R_{16} is C_{1-6} alkyl.

10. The compound of claim 9, wherein the optionally substituted heterocycle is optionally substituted N-morpholinyl, N-pyrrolidinyl or N-piperazinyl.

11. The compound of claim 1, wherein Het is (iii), (iv) or (v), R_1 is H or alkyl and R_2 and R_3 are both hydrogen.

12. The compound of claim 1, wherein Het is (vi), R_1 is hydrogen, R_2 is selected from the group consisting of aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, and R_3 and R_4 are both hydrogen.

13. The compound of claim 1, wherein Het is (vii), (viii), (ix) or (x), R_2 is hydrogen or aminocarbonyl, and R_3 is hydrogen.

14. The compound of claim 1, wherein R_2-R_4 are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, amino(C_1-C_6)alkyl, amino, C_1-C_6 alkylthio, cyano, C_1-C_6 alkylsulfinyl, hydroxy(C_1-C_6)alkyl, C_1-C_6 alkoxy, aminocarbonyl, C_1-C_6 alkylaminocarbonyl, C_6-C_{10} arylaminocarbonyl, C_6-C_{10} aryl(C_1-C_6)alkylamino-carbonyl, C_1-C_6 alkylcarbonylamino, C_6-C_{10} arylcarbonylamino, C_6-C_{10} aryl(C_1-C_6)alkylcarbonylamino, C_1-C_6

alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, C_1-C_6 alkylaminosulfonyl. C_1-C_6 alkylsulfonyl and heterocyclosulfonyl.

15. The compound of claim 14, wherein R_2-R_4 are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino(C_1-C_6)alkyl, C_1-C_6 alkylthio and aminocarbonyl.

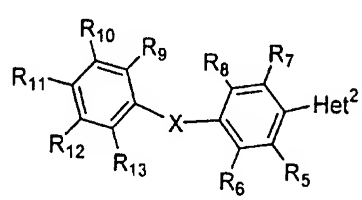
16. The compound of claim 1, wherein R_5-R_{13} are independently selected from the group consisting of include hydrogen, halo, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_4-C_7 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl(C_1-C_6)alkyl, C_6-C_{10} aryl(C_2-C_6)alkenyl, C_6-C_{10} aryl(C_2-C_6)alkynyl, C_1-C_6 hydroxyalkyl, nitro, amino, ureido, cyano, C_1-C_6 acylamido, hydroxy, thiol, C_1-C_6 acyloxy, azido, C_1-C_6 alkoxy, and carboxy.

17. The compound of claim 16, wherein R_5-R_8 are all hydrogen.

18. The compound of claim 1, wherein X is O or S.

19. The compound of claim 18, wherein X is O.

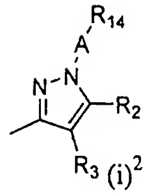
20. The compound of claim 1, having the Formula ***II***:



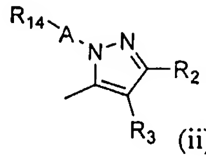
II

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

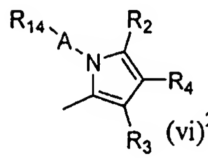
Het^2 is selected from the group consisting of



$(i)^2$;



$(ii)^2$ and



$(vi)^2$;

A is selected from the group consisting of C(O), $CH_2C(O)$, S(O) and SO_2;

R_{2-15} are as defined in claim 1; and

X is O or S,

with the proviso that when Het^2 is $(i)^2$ or $(ii)^2$

a) X is O, R_2 is methylthio, R_1 is H or $C(O)R_{14}$ wherein R_{14} is optionally substituted phenyl, at least one of R_5-R_{13} is other than H; or

b) R_1 is $C(O)NH_2$ and X is O, at least one of R_2, R_3 and R_5-R_{13} is other than H.

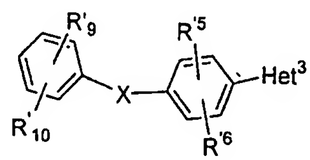
21. The compound of claim 20, wherein R_{14} is amino, optionally substituted C_1-C_6 alkylamino, optionally substituted C_1-C_6 alkyl, or optionally substituted heterocycle; R_2, R_3, and R_4 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylthio or C_1-C_6 alkylsulfinyl; and X is O; with the proviso that the compound is not 3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide.

22. The compound of claim 20, wherein A is C(O) or $CH_2C(O)$, X is O and R_{14}, R_2, R_3, and R_4 are as defined in claim 1.

23. The compound of claim 20, wherein A is S(O) or SO_2, R_2-R_4 are independently H or C_{1-6} alkyl and X is O.

24. The compound of claim 20, wherein A is S(O) or SO_2, R_2-R_4 are H, R_{14} is methyl and X is O.

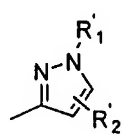
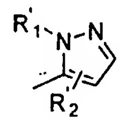
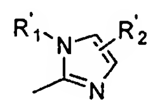
25. The compound of claim 1, having Formula *III*:



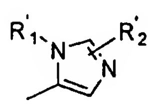
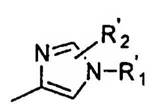
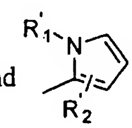
III

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

Het^3 is selected from the group consisting of

 ;  ;  ;

(i)^3 (ii)^3 (iii)^3

 ;  and  ;

(iv)^3 (v)^3 (vi)^3

R'_1 is selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14};

R'_2 is attached to a carbon atom that is not the linking atom attached to the aryl group and is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cyano, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino,

aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl;

R'_5, R'_6, R'_9, and R'_{10} are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkenyl, heterocycle, heterocycloalkyl, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$ where R_{15} is defined as above, with the following provisos that:

1) when Het is $(i)^3$ or $(ii)^3$,

a) R'_1 is H and X is O or S, at least one of R'_2, R'_5, R'_6, R'_9 and R'_{10} is other than H, except that R'_9 or R'_{10} is not NO_2 when R'_2 is CH_3, and R'_2 is not $-CH_2CH_2COOH$ when the other substituents are each H;

b) R'_1 is H, X is O and R'_9 or R'_{10} is NO_2 or OCH_3, at least one of the other substituents is other than H;

c) X is O, R'_9 and R'_{10} are CN and a Cl group *ortho* to CN, at least one of R'_2, R'_5 or R'_6 is other than H;

d) X is O, R'_5 and R'_9 are Cl, at least one of R'_6 or R'_{10} is other than H;

e) X is O, R'_2 is methylthio, R'_1 is H or $C(O)R_{14}$ wherein R_{14} is optionally substituted phenyl, at least one of R'_5, R'_6, R'_9 or R'_{10} is other than H; or

f) R'_1 is $C(O)NH_2$ and X is O, at least one of R'_2, R'_5, R'_6, R'_9 or R'_{10} is other than H;

2) when Het is (iii)[3], R'_1 is H and X is O, R'_5, R'_6, R'_9 or R'_{10} are not all H;

3) when Het is (iv)[3] and R'_1 is H or alkyl, R'_5, R'_6, R'_9 or R'_{10} are not all H; or

4) when Het is (vi)[3], R'_1 is H and X is O or S, R'_5, R'_6, R'_9 or R'_{10} are not all H.

26. The compound of claim 25, wherein X is O or S.

27. The compound of claim 25, wherein Het^3 is (i)[3] or (ii)[3] and R'_1 is heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, or SO_2R_{14} wherein R_{14} is amino, alkyl, alkylamino or heterocycle, all of which can be optionally substituted.

28. The compound of claim 27, wherein wherein R_{14} is amino.

29. The compound of claim 25, wherein Het^3 is (vi)[3], R'_1 is hydrogen and R'_2 is selected from the group consisting of aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl.

30. The compound of claim 29, wherein R'_2 is aminocarbonyl.

31. The compound of claim 25, wherein R'_2 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, carboxy(C_1-C_6)alkyl, C_1-C_6 alkylamino,

aminocarbonyl, C_1-C_6 alkylaminocarbonyl, C_1-C_6 alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, C_1-C_6 alkylaminosulfonyl, C_1-C_6 alkylsulfonyl and heterocyclosulfonyl.

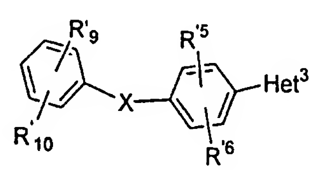
32. The compound of claim 31, wherein R'_2 is hydrogen or aminocarbonyl.

33. The compound of claim 25, wherein R'_5, R'_6, R'_9, and R'_{10} are independently selected from the group consisting of hydrogen, halo, halo(C_1-C_6)alkyl, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, alkoxy(C_1-C_6)alkyl, nitro, amino, C_1-C_6 acylamino, amide, hydroxy, thiol, C_1-C_6 acyloxy, C_1-C_6 alkoxy, carboxy, carbonylamido and C_1-C_6 alkylthiol.

34. The compound of claim 25, wherein R'_2 is attached to a carbon atom adjacent to a nitrogen atom when Het^3 is $(i)^3$, $(ii)^3$ or $(vi)^3$.

35. The compound of claim 25, wherein Het^3 is selected from the group consisting of $(i)^3$, $(ii)^3$, $(iii)^3$, $(iv)^3$ and $(v)^3$.

36. The compound having Formula ***III***:



III

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

Het^3 is $(i)^3$ or $(ii)^3$;

R'_1 is $C(O)R_{14}$;

R'_2 is attached to a carbon atom that is not the linking atom attached to the aryl group and is selected from the group consisting of hydrogen, alkyl,

alkenyl, alkynyl, cyano, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl;

R'_5, R'_6, and R'_{10} are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

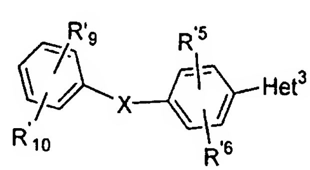
R'_9 is selected from the group consisting of halo, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkenyl, heterocycle, heterocycloalkyl, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$ where R_{15} is hydrogen, alkyl or cycloalkyl.

37. The compound having Formula *III*:



III

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

Het^3 is $(iii)^3$, $(iv)^3$, $(v)^3$ or $(vi)^3$;

R'_1 is selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14};

R'_2 is attached to a carbon atom that is not the linking atom attached to the aryl group and is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cyano, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl;

R'_5, R'_6, and R'_{10} are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

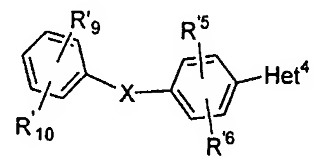
R'_9 is selected from the group consisting of halo, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkenyl, heterocycle, heterocycloalkyl, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$ where R_{15} is hydrogen, alkyl or cycloalkyl.

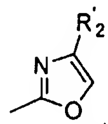
38. The compound of claim 1, having Formula *IV*:



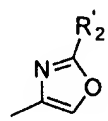
IV

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

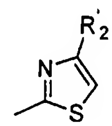
Het[4] is selected from the group consisting of



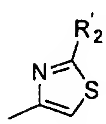
(vii)[4] ;



(viii)[4] ;



(ix)[4] and



(x)[4] ;

R'_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cyano, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl;

R'_5, R'_6, R'_9, and R'_{10} are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano,

acylamino, amide, hydroxy, thiol, acyloxy, azido. alkoxy, carboxy, carbonylamido and alkylthiol; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$ where R_{15} is defined as above.

39. The compound of claim 38, wherein Het^4 is $(vii)^4$ or $(x)^4$.

40. The compound of claim 1, wherein said compound is:

3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

5-methylthio-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide;

5-methylsulfinyl-3-(4-phenoxyphenyl)-1H-pyrazole-1-carboxamide;

3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-methoxyphenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-aminophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(3-chloro-2-cyanophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(2,4-difluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-chloro-2-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(2-chloro-4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

1-[3-[4-(4-nitrophenoxy)phenyl]-1H-pyrazolyl]ethanone;

2-methyl-1-[3-(4-phenoxyphenyl)-1H-pyrazole]propanone;

1-methanesulfonyl-3-(4-phenoxy)phenyl-1H-pyrazole;

2-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-1-(4-methyl)piperazin-1-yl-ethanone;

1-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-2-methyl-propan-2-ol;

1-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-propan-2-one;

1-morpholin-4-yl-2-{5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazol-1-yl}-ethanone;

1-[2-(methanesulfonylamino)ethyl]-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

1-(2-carbamoyloxyethyl)-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

3-[4-(4-fluorophenylthio)phenyl]-1H-pyrazole-1-carboxamide;

3-[4-(4-fluorophenylthio)phenyl]-1H-pyrazole;

2-[5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl]ethanol;

3-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxylic acid dimethylamide;

1-benzyl-5-[4-(4-fluorophenoxy)phenyl]-1H-pyrazole;

2-[3-[4-(4-fluorophenoxy)phenyl]-2H-pyrazol-2-yl]-1-pyrrolidin-1-yl ethanone;

2-(*N*-methylacetamido)-3-[4-(4-fluorophenoxy)phenyl]-2H-pyrazole;

2-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-acetamide;

2-{3-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-acetamide;

3-{5-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-propionamide;

3-[3-fluoro-4-(4-fluorophenoxy)phenyl]-1H-pyrazole-1-carboxamide;

2-{3-[4-(4-fluorophenoxy)phenyl]-pyrazol-1-yl}-pyrimidine;

2-{3-[4-(4-trifluoromethylphenoxy)phenyl]pyrazol-1-yl}pyrimidine;

4-[4-(4-fluorophenoxy)phenyl]-1H-imidazole;

4-[4-(4-fluorophenoxy)-3-fluorophenyl]-1H-imidazole;

4-[4-(2,4-difluorophenoxy)phenyl]-1H-imidazole;

4-[4-(2-fluoro-4-chlorophenoxy)phenyl]-1H-imidazole;

4-(4-(4-trifluoromethylphenoxy)phenyl]-1H-imidazole;

4-[4-(2,4-difluorophenoxy)phenyl]-2-methyl-1H-imidazole;

4-[4-(2,4-difluorophenoxy)phenyl]-1-methyl-1H-imidazole-2-carboxamide;

2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole;

2-[4-(4-fluorophenoxy)phenyl]-1H-benzimidazole;

2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole-4-carboxamide;

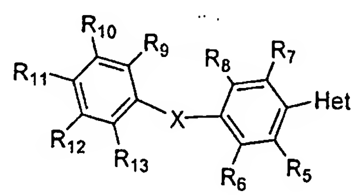
2-[4-(4-fluorophenoxy)phenyl]-1H-imidazole-4-carbonitrile;

5-[4-(4-fluorophenoxy)phenyl]-pyrrole-2-carboxamide;

5-(4-phenoxyphenyl)pyrrole-2-carboxamide;
methyl 5-[4-(4-fluorophenoxy)phenyl]pyrrole-2-carboxylate;
2-[4-(4-fluorophenoxy)phenyl]oxazole-4-carboxamide; and
4-[4-(4-fluorophenoxy)-3-fluorophenyl]thiazole-2-carboxamide
or a pharmaceutically acceptable salt thereof.

41. A pharmaceutical composition, comprising the compound of any one of claims 1-40 and a pharmaceutically acceptable carrier or diluent.

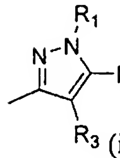
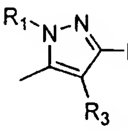
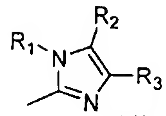
42. A method of treating a disorder responsive to the blockade of sodium channels in a mammal suffering therefrom, comprising administering to a mammal in need of such treatment an effective amount of a compound of formula:

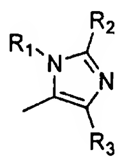
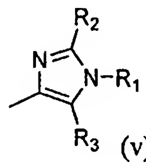
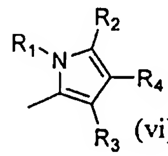


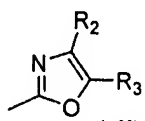
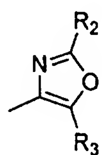
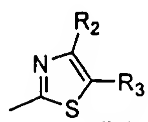
I

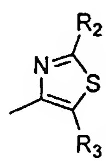
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Het is a heteroaryl selected from the group consisting of

 (i) ;  (ii) ;  (iii) ;

 (iv) ;  (v) ;  (vi) ;

 (vii) ;  (viii) ;  (ix) and

 (x) ;

R_1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14} all of which may be optionally substituted;

R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, cyano, amino, alkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, or the R groups in adjacent carbon atoms can be taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or

partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; or R_9 and R_{10} or R_{10} and R_{11} are taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

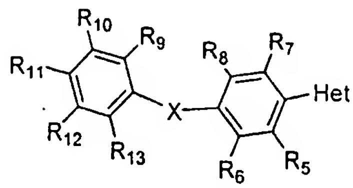
R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkynyl, arylalkylamino, dialkylaminoalkenyl, heterocycle, heterocycloalkylamino, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$, wherein R_{15} is hydrogen, alkyl or cycloalkyl.

43. The method of claim 42, wherein the compound administered is as claimed in any one of the claims 1-40.

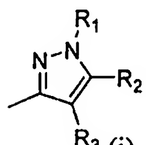
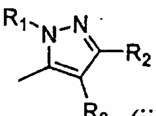
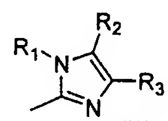
44. A method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating neurodegenerative conditions; treating, preventing or ameliorating pain or tinnitus; treating, preventing or ameliorating manic depression; providing local anesthesia; or treating arrhythmias, or treating convulsions, comprising administering to a mammal in need of such treatment an effective amount of a compound formula:

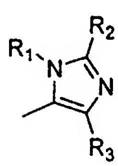
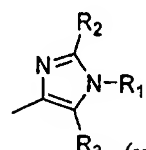
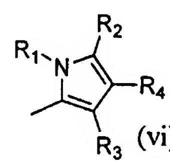


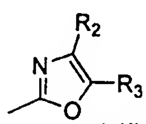
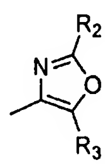
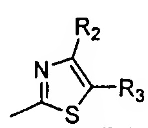
I

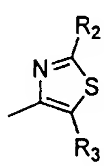
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Het is a heteroaryl selected from the group consisting of

 (i) ;  (ii) ;  (iii) ;

 (iv) ;  (v) ;  (vi) ;

 (vii) ;  (viii) ;  (ix) and

 (x) ;

R_1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14} all of which may be optionally substituted;

R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, cyano, amino, alkylamino, aminocarbonyl, alkylaminocarbonyl,

arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, or the R groups in adjacent carbon atoms can be taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; or R_9 and R_{10} or R_{10} and R_{11} are taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkynyl, arylalkylamino, dialkylaminoalkenyl, heterocycle, heterocycloalkylamino, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

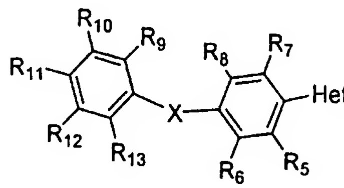
R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$, wherein R_{15} is hydrogen, alkyl or cycloalkyl.

45. The method of claim 44, wherein the compound administered is as claimed in any one of claims 1-40.

46. The method of claim 44, wherein the method is for treating, preventing or ameliorating pain and said pain is one of neuropathic pain, surgical pain or chronic pain.

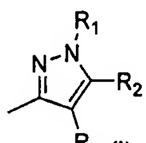
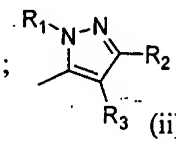
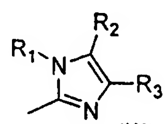
47. A method of alleviating or preventing seizure activity in an animal subject, comprising administering to said animal in need of such treatment an effective amount of a compound of formula:

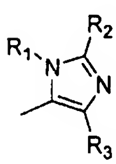
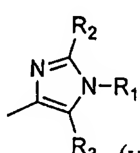
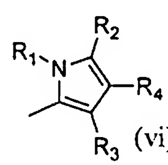


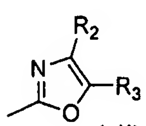
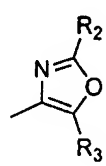
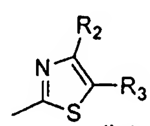
I

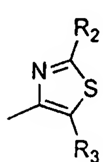
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Het is a heteroaryl selected from the group consisting of

 (i) ;  (ii) ;  (iii) ;

 (iv) ;  (v) ;  (vi) ;

 (vii) ;  (viii) ;  (ix) and

 (x) ;

R_1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14} all of which may be optionally substituted;

R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, cyano, amino, alkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, or the R groups in adjacent carbon atoms can be taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; or R_9 and R_{10} or R_{10} and R_{11} are taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

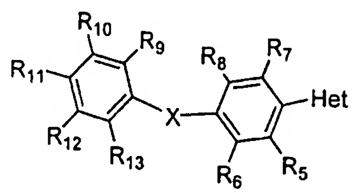
R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkynyl, arylalkylamino, dialkylaminoalkenyl, heterocycle, heterocycloalkylamino, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$, wherein R_{15} is hydrogen, alkyl or cycloalkyl.

48. The method of claim 47, wherein the compound administered is as claimed in any one of claims 1-40.

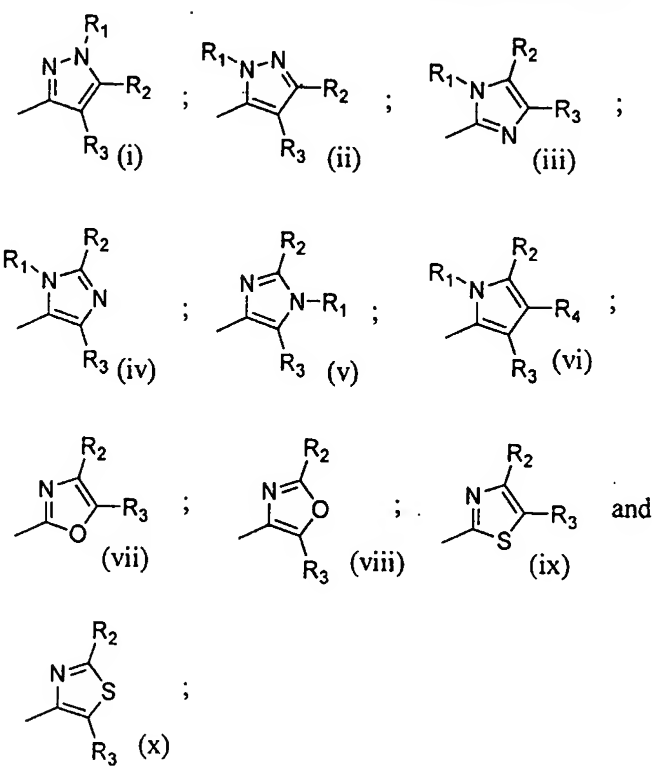
49. The compound having the formula:



I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Het is a heteroaryl selected from the group consisting of



R_1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, $C(O)R_{14}$, $CH_2C(O)R_{14}$, $S(O)R_{14}$, and SO_2R_{14} all of which may be optionally substituted;

R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, haloalkyl, aryl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, cyano, amino, alkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, heterocyclocarbonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonyl, and heterocyclosulfonyl, or the R groups in adjacent carbon atoms can be taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, and R_{13} are independently selected from the group consisting of hydrogen, halo, haloalkyl, aryl, cycloalkyl, saturated or partially unsaturated heterocycle, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkylalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; or R_9 and R_{10} or R_{10} and R_{11} are taken together with the carbon atoms to which they are attached to form a carbocycle or a heterocycle;

R_{14} is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR_{16}, alkylamino, dialkylamino, alkenylamino, cycloalkyl, aralkyl, aryl, heteroaryl, arylalkenyl, arylalkynyl, arylalkylamino, dialkylaminoalkenyl, heterocycle, heterocycloalkylamino, and cycloalkylalkylamino, all of which can be optionally substituted; wherein

R_{16} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

X is one of O, S, NR_{15}, CH_2, $NR_{15}C(O)$, or $C(O)NR_{15}$, wherein R_{15} is hydrogen, alkyl or cycloalkyl,

wherein said compound is ^{3}H or ^{14}C radiolabeled.

50. Use of a compound of claim 49 as a radioligand for its binding site on the sodium channel.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07944

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HILBORN, J.G. et al. Poly(aryl ether-benzoxazoles). Maromolecules. 1990, Vol. 23, No. 11, pages 2854-2861, especially compound 2 on page 2857.	1,16-191,1
X	HEDRICK, J.L. Imide-aryl ether benzothiazoles. Polymer. 1992, Vol. 33, No. 7, pages 1399-1405, especially compound 2 on page 1402.	1, 16-19
X	RADWAN, S.M. Synthesis and reactions of some diphenylsulfides. Collect. Czech. Chem. Commun. 1992, Vol. 57, pages 1553-1558, especially compounds III, IV, Xa and Xc in table on page 1554.	1, 18, 38, 39

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 MAY 2000	15 AUG 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Cynthia Lawrence for CHANA AULAKH
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07944

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,769,062 A (LANGE et al) 06 September 1988 (6.10.88), especially compounds 17 and 19 in column 4, lines 62-64.	1
X	US 4,540,648 A (SCHELER) 10 September 1985 (10.9.85), especially compound 18 in column 15.	1
X	JP 7-25849 A (HAGIWARA, K. et al.) 27 January 1995 (27.01.95), especially compound 9 in table 1 on page 5.	1, 16-19
X	WO 98/40364 A1 (G.D. SEARLE AND CO.) 17 September 1998 (17.09.98), especially example 4 on page 16, compound (c) on page 27 and compound (d) on page 28.	1, 13-19, 38, 39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07944

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07944

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 31/40, 31/415, 31/421, 31/426, 31/496, 31/506, 31/4164, 31/5377; C07D 207/20, 231/10, 233/54, 403/00, 413/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/231.5, 255, 256, 365, 374, 395, 396, 397, 406, 408, 423, 427 ; 544/140, 242, 371 ; 548/205, 236, 304.4, 338.1, 373.1, 537

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/231.5, 255, 256, 365, 374, 395, 396, 397, 406, 408, 423, 427 ; 544/140, 242, 371 ; 548/205, 236, 304.4, 338.1, 373.1, 537

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. The species are as follows:

I. Compounds of formula I where X represents O, S, N or CH2 and Het represents structures (i), (ii), (iii), (iv) or (v), pharmaceutical compositions containing these compounds and a method of using these compounds.

II. Compounds of formula I where X represents C(O)N or N-C(O) and Het represents structures (i), (ii), (iii), (iv) or (v), pharmaceutical compositions containing these compounds and a method of using these compounds.

III. Compounds of formula I where X represents O, S, N or CH2 and Het represents structure (vi), pharmaceutical compositions containing these compounds and a method of using these compounds.

IV. Compounds of formula I where X represents C(O)N or N-C(O) and Het represents structure (vi), pharmaceutical compositions containing these compounds and a method of using these compounds.

V. Compounds of formula I where X represents O, S, N or CH2 and Het represents structures (vii) or (viii), pharmaceutical compositions containing these compounds and a method of using these compounds.

VI. Compounds of formula I where X represents C(O)N or N-C(O) and Het represents structures (vii)or (viii), pharmaceutical compositions containing these compounds and a method of using these compounds.

VII. Compounds of formula I where X represents O, S, N or CH2 and Het represents structures (ix) or (x), pharmaceutical compositions containing these compounds and a method of using these compounds.

VIII. Compounds of formula I where X represents C(O)N or N-C(O) and Het represents structures (ix)or (x), pharmaceutical compositions containing these compounds and a method of using these compounds.

The claims are deemed to correspond to the species listed above in the following manner:

Species I and II : Claims 4, 11 and 36

Species III : Claim 12

Species V, VI, VII and VIII : Claims 13, 38 and 39

The following claims are generic: Claims 1-3, 5-10, 14-35, 37 and 40-50

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07944

There is no common core which in the Markush Practice, is a significant structural element shared by all of the alternatives; see PCT Administrative Instructions Annex B Part 1 (f) (i) (B) (1).